# PREFACE

2022 marked a significant step in realizing Sidra Medicine's research mission to deliver hospital-wide precision medicine, with research technologies and innovation continuing to play a prominent role in every patient's journey.

Indeed, by leveraging the lessons learned from the pandemic, we were able to accelerate the integration of research into clinical care pathways, enabling our researchers to take a more detailed view of individual patient challenges, and facilitating more flexible, responsive, and innovative translational research. The impact of research on patient care was seen at multiple levels, from diagnosis onwards, and as much as 57 percent of our research studies had a clinical lead.

The pandemic highlighted too the need for research funding, and we are pleased to confirm that grants increased in 2022, with 15 total grants from Qatar National Research Fund and external funds, totaling almost QR11 million. Included among these are two major international grants from the Juvenile Diabetes Research Foundation (JDRF), which funds leading scientists across the world to deliver possible cures and life-improving breakthroughs in the fight against type 1 diabetes. The JDRF grants will fund two research projects with Sidra Medicine scientists to advance predictions of type 1 diabetes among susceptible children using emerging technologies.

The last year also saw our scientists and clinicians publishing more than 250 papers, with close to 50 percent of Research Branch publications appearing in the top 15 percent of international journals. It is with pride that we note that three Research Branch publications appeared on the covers of international journals, The Lancet Oncology, Nanoscale and Advanced Materials: a groundbreaking study on pediatric cancer tumors; an in-depth study that indicates fasting as a possible immunotherapy for treating cancer; and a largescale genomic study co-led by Sidra Medicine researchers that helped unveil cancer susceptibility among Arab and Middle Eastern populations. The latter study is the first of its kind in the region and used state-of-the-art bioinformatics and statistical genetics methods to analyze the genomes of more than 6,000 Qataris, representing a remarkable national effort to understand the genetic basis of cancer.

We are also pleased to confirm a Memorandum of Understanding (MoU) signed with Microsoft to facilitate our digital transformation goals at a time when we are scaling up our genomic research capabilities. Such transformation will enable our scientists to perform complex data operations and build an ecosystem that can facilitate genomics computing. In alignment with Sidra Medicine's commitment to capacity building, we continued to facilitate invaluable work experience, skills development and networking opportunities for young adults beginning their careers in science, medicine and public health, training more than 60 students and mentoring four PhD students to graduation.

In all, 2022 represents a year of innovation and making precision medicine a reality. We extend our appreciation to all who remained focused on helping us deliver on this mission, not just for the good of our patients and their families, but for the benefit of future generations.

*Editor-in-Chief*
**Dr. Khalid A. Fakhro**
Chief Research Officer

*Managing Editor*
**Noor Faisal**
Manager - Research Outcomes

# المقدمة

لقد كانت سنة ٢٠٢١ مليئة بالتحديات على أصعدة متعددة: فلم يتعافَ العالم بعد من تبعات الوباء العالمي، وخيّم الشك على مستقبل الوباء، وما ترتب على ذلك من الأعباء الثقيلة الواقعة على مؤسسات الرعاية الصحية، بالإضافة إلى حالة القلق والحذر التي اكتنفت جميع أفراد المجتمع مما جعل التكيف مع أسلوب الحياة الجديد أمرًا مرهقًا للغاية. لكن من المفارقات التي شهدناها أنه وعلى الرغم من تباعد المسافات والآراء، فإن البشرية لم تتحد من قبل بهذا الشكل في مواجهة عدوٍ مشترك. ولم نكن نعلم أن محنة هذا الوباء العالمي، مهما وضعت من تحديات، ستكون منحة خفية لمجال العلوم الصحية والأبحاث الحيوية... ومع تركيز العالم على البيولوجيا وانصباب اهتمامه على الصحة العامة فقد أصبحت مصطلحات مثل عدد التكاثر الأساسي (R )، وتفاعل البوليمريز المتسلسل اللحظي (RT-PCR)، وقيمة عتبة الدورة (Ct value)، والحمض النووي الريبي (RNA)، وغيرها، جزءا من الحوار العام بعد أن كانت من قبل مقتصرة على فئة محدودة من ذوي الاختصاص والعلوم! ... واستحوذ الفضول المعرفي والرغبة في التساؤل على انتباه الجمهور الذي أصبح على متابعة مستمرة لمجريات الدراسات العلمية ونتائجها.

وبصفتنا كمركز طبي أكاديمي وطني، حقق فرع سدرة للأبحاث إنجازات مهمة خلال فترة الوباء. فمن جهة، طور مختبر الجينوم الأساسي لدينا طرقًا مبتكرة لاستخلاص واكتشاف الحمض النووي الفيروسي، مكنتنا من تجاوز أزمة النقص العالمي في سلاسل التوريد لمواد الاختبار. ومن جهة أخرى، انضم علماؤنا إلى اتحادات عالمية وفرق بحثية مرموقة لدراسة انتشار وتنوع كوفيد- ١٩ لدى البالغين والأطفال، مما خلُص إلى اكتشافات تركت أثرًا على الرعاية السريرية في جميع أنحاء العالم. ومع بدء طرح اللقاحات، طورت وحدة التنميط الظاهري فحصًا مبتكرًا يكتشف مستضدات جميع أنواع فيروسات كورونا البشرية.

وبعيدًا عن مشروعات كوفيد- ١٩، حظي فرع الأبحاث بعام مليء بالنجاحات. فقد التحق أكثر من ٦٠٠٠ من المرضى وأسرهم بالدراسات البحثية. كما نشر أطباء سدرة وعلماؤها قرابة ٣٠٠ ورقة علمية؛ وكانت ٨٥٪ من هذه الابحاث منشورة في أفضل ١٥٪ من الدوريات العلمية العالمية. وعلى رأس هذه الانجازات، فإن سدرة للطب حصل على ١٢ منحة بحثية تقدر ب ٧.٣ ملايين ريال قطري، مما يُظهر أهمية الدور الرائد الذي تلعبه المراكز الطبية الأكاديمية في نمو البحث العلمي في دولة قطر.

وعلى صعيد المساهمة في الاقتصاد المعرفي، واصل سدرة للطب تنمية المتدربين في مجالات الطب والأبحاث الحيوية، حيث حظي ٦٠٪ تقريبًا من الباحثين على تعيين أكاديمي في مؤسسات محلية وعالمية، وأصبح ٥٢ فردًا من المتدربين والطلاب جزءًا من أسرة سدرة للبحوث في عام ٢٠٢١. واستضاف مركز الابحاث ما يقارب ٢٠ من طلاب الماجستير والدكتوراه في مختبراته لدعم نمو المواهب الصاعدة وتطويرها لقيادة هذا المجال في المستقبل. وأخيرًا، فقد استضاف سدرة للطب ندوته السنوية (الطب الدقيق وعلم الجينوم الوظيفي) في نسخته السابعة هذا العام بشكل افتراضي مُظهرين التزامنا بالتعليم والاستدامة وبناء مؤسسة بحثية في قطر تربطها روابط قوية مع المجتمع العلمي العالمي.

وفي الختام، فقد كان عام ٢٠٢١ أحد أكثر الأعوام إنتاجًا وابتكارًا بالنسبة لمركز الأبحاث في سدرة للطب. ونحن ندين بخالص الامتنان لفرق باحثينا الذين يعملون بجد ومثابرة، والذين تصدوا للوباء وعملوا بشكل دؤوب على مدار الساعة لضمان الحفاظ على جذوة الاكتشاف والابتكار، ولمختلف الزملاء السريريين الذين لعبوا دورًا أساسيًا في تطوير الدراسات وترجمة النتائج لمصلحة المرضى، ولجميع الأسر والمرضى الذين وضعوا ثقتهم في سدرة للطب لتقديم أجود رعاية قائمة على الطب الأكاديمي والأبحاث.

نتمنى أن تجدوا بين صفحات هذا التقرير قصصًا ملهمة واكتشافاتٍ رائدة ونقطة انطلاق الى مستقبل مشرق بإذن الله.

**الدكتور خالد فخرو**
رئيس قسم الأبحاث

**نور فيصل**
مدير التحرير

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RESEARCH ARTICLE

# Fasting-Mimicking Diet Is Safe and Reshapes Metabolism and Antitumor Immunity in Patients with Cancer

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**ABSTRACT** In tumor-bearing mice, cyclic fasting or fasting-mimicking diets (FMD) enhance the activity of antineoplastic treatments by modulating systemic metabolism and boosting antitumor immunity. Here we conducted a clinical trial to investigate the safety and biological effects of cyclic, five-day FMD in combination with standard antitumor therapies. In 101 patients, the FMD was safe, feasible, and resulted in a consistent decrease of blood glucose and growth factor concentration, thus recapitulating metabolic changes that mediate fasting/FMD anticancer effects in preclinical experiments. Integrated transcriptomic and deep-phenotyping analyses revealed that FMD profoundly reshapes anticancer immunity by inducing the contraction of peripheral blood immunosuppressive myeloid and regulatory T-cell compartments, paralleled by enhanced intratumor Th1/cytotoxic responses and an enrichment of IFNγ and other immune signatures associated with better clinical outcomes in patients with cancer. Our findings lay the foundations for phase II/III clinical trials aimed at investigating FMD antitumor efficacy in combination with standard antineoplastic treatments.

**SIGNIFICANCE:** Cyclic FMD is well tolerated and causes remarkable systemic metabolic changes in patients with different tumor types and treated with concomitant antitumor therapies. In addition, the FMD reshapes systemic and intratumor immunity, finally activating several antitumor immune programs. Phase II/III clinical trials are needed to investigate FMD antitumor activity/efficacy.

## INTRODUCTION

In tumor-bearing mice, cyclic fasting or calorie-restricted, low-carbohydrate, low-protein diets, collectively referred to as fasting-mimicking diets (FMD), have convincingly demonstrated additive or synergistic antitumor activity in combination with cytotoxic chemotherapy (ChT), immunotherapy, or endocrine therapies (1–6). These anticancer effects are mostly mediated by fasting/FMD-induced reduction of blood glucose, insulin, and insulin-like growth factor 1 (IGF1) concentration, which results in the inhibition of anabolic processes that sustain unrestrained growth/proliferation and the repair of chemotherapy-induced genotoxic and proteotoxic effects in cancer cells (2, 6). More recently, fasting and FMD were shown to boost tumor infiltration by $CD8^+$ T cells—the effectors of antitumor immune responses—and to reduce immunosuppressive regulatory T cells (Treg) in syngeneic mouse models (3, 5).

On the basis of this preclinical evidence, clinical trials have been initiated to investigate the feasibility and antitumor activity of cyclic FMD in combination with standard antitumor therapies in different clinical contexts (NCT03709147, NCT04248998, NCT03700437). The only study whose results have been reported so far is the phase II trial "DIRECT" (NCT02126449), which was prematurely interrupted because of poor patient compliance with the proposed FMD regimen and because the FMD failed to reduce ChT-induced adverse events (7).

Here we report on the final results of a first-in-human clinical trial (NCT03340935) that investigated the safety, feasibility, and metabolic and immunomodulatory effects of a severely calorie-restricted, five-day FMD regimen in patients with cancer. We also report on results of an interim analysis in which we investigated FMD-induced systemic and intratumor immune responses in 22 patients with breast cancer enrolled in the ongoing DigesT trial (NCT03454282).

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# Changes in the stool and oropharyngeal microbiome in obsessive-compulsive disorder

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**Although the etiology of obsessive–compulsive disorder (OCD) is largely unknown, it is accepted that OCD is a complex disorder. There is a known bi-directional interaction between the gut microbiome and brain activity. Several authors have reported associations between changes in gut microbiota and neuropsychiatric disorders, including depression or autism. Furthermore, a pediatric-onset neuropsychiatric OCD-related syndrome occurs after streptococcal infection, which might indicate that exposure to certain microbes could be involved in OCD susceptibility. However, only one study has investigated the microbiome of OCD patients to date. We performed 16S ribosomal RNA gene-based metagenomic sequencing to analyze the stool and oropharyngeal microbiome composition of 32 OCD cases and 32 age and gender matched controls. We estimated different α- and β-diversity measures and performed LEfSe and Wilcoxon tests to assess differences in bacterial distribution. OCD stool samples showed a trend towards lower bacterial α-diversity, as well as an increase of the relative abundance of *Rikenellaceae*, particularly of the genus *Alistipes*, and lower relative abundance of *Prevotellaceae*, and two genera within the *Lachnospiraceae*: *Agathobacer* and *Coprococcus*. However, we did not observe a different Bacteroidetes to Firmicutes ratio between OCD cases and controls. Analysis of the oropharyngeal microbiome composition showed a lower Fusobacteria to Actinobacteria ratio in OCD cases. In conclusion, we observed an imbalance in the gut and oropharyngeal microbiomes of OCD cases, including, in stool, an increase of bacteria from the *Rikenellaceae* family, associated with gut inflammation, and a decrease of bacteria from the *Coprococcus* genus, associated with DOPAC synthesis.**

Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder characterized by intrusive and unwanted thoughts (termed obsessions) and repetitive behaviors or mental acts (called compulsions) that are performed to partially relieve the anxiety or distress caused by the obsessions. The etiology of OCD is largely unknown, although it likely involves a combination of genetic, neurobiological and environmental factors or events. Genetic association studies, including genome-wide association analysis and a multispecies approach integrating

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ORIGINAL ARTICLE

# Inherited IFNAR1 Deficiency in a Child with Both Critical COVID-19 Pneumonia and Multisystem Inflammatory Syndrome

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## Abstract

**Background** Inborn errors of immunity (IEI) and autoantibodies to type I interferons (IFNs) underlie critical COVID-19 pneumonia in at least 15% of the patients, while the causes of multisystem inflammatory syndrome in children (MIS-C) remain elusive.

**Objectives** To detect causal genetic variants in very rare cases with concomitant critical COVID-19 pneumonia and MIS-C.

**Methods** Whole exome sequencing was performed, and the impact of candidate gene variants was investigated. Plasma levels of cytokines, specific antibodies against the virus, and autoantibodies against type I IFNs were also measured.

**Results** We report a 3-year-old child who died on day 56 of SARS-CoV-2 infection with an unusual clinical presentation, combining both critical COVID-19 pneumonia and MIS-C. We identified a large, homozygous loss-of-function deletion in *IFNAR1*, underlying autosomal recessive IFNAR1 deficiency.

**Conclusions** Our findings confirm that impaired type I IFN immunity can underlie critical COVID-19 pneumonia, while suggesting that it can also unexpectedly underlie concomitant MIS-C. Our report further raises the possibility that inherited or acquired dysregulation of type I IFN immunity might contribute to MIS-C in other patients.

**Keywords** COVID-19 · critical pneumonia · multisystem inflammatory syndrome in children (MIS-C) · inborn errors of immunity (IEI) · primary immunodeficiency (PID) · IFNAR1

## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is asymptomatic or mild, i.e., restricted to the upper respiratory tract in about 70% of the cases [1, 2]. Moderate, non-hypoxemic pneumonia is seen in about 20% of the cases. More severe complications associated with the SARS-CoV-2 infection include severe pneumonia (about 10%), which can evolve into critical pneumonia, i.e., acute respiratory distress syndrome (ARDS, about 3%). Globally, the infection fatality rate is around 1%, but the risk of death doubles every 5 years from childhood onward, ranging from 0.001% at age 5 years to 10% at age 85 years [3, 4]. Autosomal recessive deficiency of IFNAR1 or IRF7 has been found in four unrelated adults with critical COVID-19 pneumonia [5]. A new patient with autosomal recessive IFNAR1 deficiency and critical COVID-19 has been recently reported [6], and a patient with TBK1 deficiency also has been identified [7]. These and other inborn errors of type I interferon (IFN) immunity had previously been reported in patients with other natural viral infections as well as in patients with live-attenuated vaccine-related viral infections [8–15]. Together with the occurrence of autoantibodies (auto-Abs)

Article summary line: Autosomal recessive IFNAR1 deficiency due to a large deletion in *IFNAR1* was identified in a 3-year-old female child who suffered from both critical COVID-19 pneumonia and MIS-C. Type I IFN signaling can be redundant in host defense against some common viruses, but defects in this pathway may also underlie life-threatening viral infections and associated complications.

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Review

# Genome sequencing data analysis for rare disease gene discovery

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## Abstract

Rare diseases occur in a smaller proportion of the general population, which is variedly defined as less than 200 000 individuals (US) or in less than 1 in 2000 individuals (Europe). Although rare, they collectively make up to approximately 7000 different disorders, with majority having a genetic origin, and affect roughly 300 million people globally. Most of the patients and their families undergo a long and frustrating diagnostic odyssey. However, advances in the field of genomics have started to facilitate the process of diagnosis, though it is hindered by the difficulty in genome data analysis and interpretation. A major impediment in diagnosis is in the understanding of the diverse approaches, tools and datasets available for variant prioritization, the most important step in the analysis of millions of variants to select a few potential variants. Here we present a review of the latest methodological developments and spectrum of tools available for rare disease genetic variant discovery and recommend appropriate data interpretation methods for variant prioritization. We have categorized the resources based on various steps of the variant interpretation workflow, starting from data processing, variant calling, annotation, filtration and finally prioritization, with a special emphasis on the last two steps. The methods discussed here pertain to elucidating the genetic basis of disease in individual patient cases via trio- or family-based analysis of the genome data. We advocate the use of a combination of tools and datasets and to follow multiple iterative approaches to elucidate the potential causative variant.

**Key words:** rare diseases; whole genome sequencing; variant interpretation; variant prioritization; next-generation sequencing; trio-analysis; bioinformatics tools; variant annotation; variant filtration; variant analysis

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REVIEW
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# Breast Milk: A Meal Worth Having

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A mother is gifted with breast milk, the natural source of nutrition for her infant. In addition to the wealth of macro and micro-nutrients, human milk also contains many microorganisms, few of which originate from the mother, while others are acquired from the mouth of the infant and the surroundings. Among these microbes, the most commonly residing bacteria are *Staphylococci, Streptococci, Lactobacilli* and *Bifidobacteria*. These microorganisms initiate and help the development of the milk microbiota as well as the microbiota of the gastrointestinal tract in infants, and contribute to developing immune regulatory factors such as cytokines, growth factors, lactoferrin among others. These factors play an important role in reducing the risk of developing chronic diseases like type 2 diabetes, asthma and others later in life. In this review, we will summarize the known benefits of breastfeeding and highlight the role of the breast milk microbiota and its cross-talk with the immune system in breastfed babies during the early years of life.

**Keywords: breastfeeding, microbiota, delivery, chronic diseases, immune system**

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## INTRODUCTION

Breast milk (BM) is the normative source of nutrition for infants in the first six months of life (1). It is considered an essential source of nutrients containing water (87%), fat (3.8%), proteins (1.0%), and lactose (7%), with both lactose and fat providing 40 and 50% of the total energy received from milk (2). BM also contains immune cells, microRNAs, hormones and bioactive compounds with anti-inflammatory, anti-infective properties (3). These include cytokines, chemokines, immunoglobulins, hormones, growth factors, oligosaccharides and antimicrobial peptides such as bacteriocin and lactoferrin (4). Studies have shown that the composition of BM varies depending on maternal and environmental factors, and is tailored to the baby's complex nutritional requirements (5).

Our understanding of the origin of milk microbiota and its role in seeding the infant's gut is still in its infancy and needs further research (6). The delivery mode appears to be an important factor in the development of the infant's gut microbiota (7, 8). Babies born via Caesarian section (C-section) are colonized by microbial communities similar to their mothers' skin microbiota, opposed to the vaginally-delivered babies whose microbiota is closer to their mothers' vaginal microbes (9). Furthermore, it is known that the rupture of the membranes during labor contributes to the early microbial seeding of the newborn (10). This transfer of microbes from the mother to her baby, during delivery, is like a "good starter kit" that will help expand the infant's microbiota.

Studies have shown that breastfed infants have higher levels of *Bifidobacterium species* in their gut, which has been attributed to the human milk oligosaccharides (HMOs) known to preferentially feed this bacterium (11, 12). This is in contrast to the formula-fed infants where the gut is inhabited by *Bacteroides*, *Firmicutes*, *Eubacterium* and *Veillonella* (13). When solid food is supplemented after 6 months of age and BM is no longer considered the major source

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RESEARCH ARTICLE

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# Qatar genome: Insights on genomics from the Middle East

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## Abstract

Despite recent biomedical breakthroughs and large genomic studies growing momentum, the Middle Eastern population, home to over 400 million people, is underrepresented in the human genome variation databases. Here we describe insights from Phase 1 of the Qatar Genome Program with whole genome sequenced 6047 individuals from Qatar. We identified more than 88 million variants of which 24 million are novel and 23 million are singletons. Consistent with the high consanguinity and founder effects in the region, we found that several rare deleterious variants were more common in the Qatari population while others seem to provide protection against diseases and have shaped the genetic architecture of adaptive phenotypes. These results highlight the value of our data as a resource to advance genetic studies in the Arab and neighboring Middle Eastern populations and will significantly boost the current efforts to improve our understanding of global patterns of human variations, human history, and genetic contributions to health and diseases in diverse populations.

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ARTICLE OPEN

# A population study of clinically actionable genetic variation affecting drug response from the Middle East

Puthen Veettil Jithesh[1]✉, Mohammed Abuhaliqa[2], Najeeb Syed[2], Ikhlak Ahmed[2], Mohammed El Anbari[2], Kholoud Bastaki[1,3], Shimaa Sherif[1], Umm-Kulthum Umlai[1], Zainab Jan[1], Geethanjali Gandhi[1,2], Chidambaram Manickam[2], Senthil Selvaraj[2], Chinnu George[2], Dhinoth Bangarusamy[1], Rania Abdel-latif[4], Mashael Al-Shafai[5], Zohreh Tatari-Calderone[2], Xavier Estivill[6], Munir Pirmohamed[7] and The Qatar Genome Program Research Consortium*

Clinical implementation of pharmacogenomics will help in personalizing drug prescriptions and alleviate the personal and financial burden due to inefficacy and adverse reactions to drugs. However, such implementation is lagging in many parts of the world, including the Middle East, mainly due to the lack of data on the distribution of actionable pharmacogenomic variation in these ethnicities. We analyzed 6,045 whole genomes from the Qatari population for the distribution of allele frequencies of 2,629 variants in 1,026 genes known to affect 559 drugs or classes of drugs. We also performed a focused analysis of genotypes or diplotypes of 15 genes affecting 46 drugs, which have guidelines for clinical implementation and predicted their phenotypic impact. The allele frequencies of 1,320 variants in 703 genes affecting 299 drugs or class of drugs were significantly different between the Qatari population and other world populations. On average, Qataris carry 3.6 actionable genotypes/diplotypes, affecting 13 drugs with guidelines for clinical implementation, and 99.5% of the individuals had at least one clinically actionable genotype/diplotype. Increased risk of simvastatin-induced myopathy could be predicted in ~32% of Qataris from the diplotypes of *SLCO1B1*, which is higher compared to many other populations, while fewer Qataris may need tacrolimus dosage adjustments for achieving immunosuppression based on the *CYP3A5* diplotypes compared to other world populations. Distinct distribution of actionable pharmacogenomic variation was also observed among the Qatari subpopulations. Our comprehensive study of the distribution of actionable genetic variation affecting drugs in a Middle Eastern population has potential implications for preemptive pharmacogenomic implementation in the region and beyond.

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## INTRODUCTION

Genetic variation plays an important role in the inter-individual differences in response to medications, and pharmacogenomic (PGx) testing has the potential to provide an informed decision on the appropriate choice and dosage of medications[1]. The current progress in next-generation sequencing (NGS) technologies provides several avenues for PGx profiling. Although many studies have promoted exome sequencing or targeted NGS panels for PGx testing at population scale[2,3], the benefits of these approaches are mostly limited by their inability to sequence the non-coding regions[4]. Whole-genome sequencing (WGS) can overcome this limitation and hence provide the most comprehensive sequencing approach for more accurate PGx profiling[5]. Furthermore, WGS provides more accurate PGx profiling through the ability to identify potential rare variants/private mutations that may affect drug disposition and response.

Resources such as the PharmVar[6,7] and Pharmacogenomics KnowledgeBase (PharmGKB)[8] and guidelines produced by the Clinical Pharmacogenetic Implementation Consortium (CPIC)[9] and the Dutch Pharmacogenetics Working Group (DPWG)[10] are helping in the clinical implementation of pharmacogenomic testing for a select number of drug-gene combinations with a high level evidence. However, prioritization and implementation of drug-gene combinations for clinical testing in different ethnic populations require the knowledge of the distribution of genetic variants affecting the drugs and prescription patterns in that population[11–13]. In addition, guidelines developed by CPIC and DPWG primarily focus on common variants, and a WGS approach would help in the identification of novel variants in the population of interest that are currently not covered by CPIC or DPWG. Although pharmacogenomic screening is established in many medical institutions in the US and Europe[14,15], such implementation is lagging in many other parts of the world, including the Middle East, due to the lack of such data[16].

Here we present the first comprehensive characterization of clinically actionable genotypes and diplotypes and their predicted phenotypic effect on efficacy, dosing and the risk of adverse events for several medications with CPIC clinical implementation guidelines in the Qatari population from the analysis of 6045 whole genomes. We also compared the distribution of these frequencies with that of other world populations represented in the 1000 genomes dataset to understand the similarities and distinctiveness of the Qatari population in their predicted response to these medications. As far as we are aware, this is the first such comprehensive study in any Middle Eastern population, with potential implications for pre-emptive pharmacogenomic implementation in the region and beyond.

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*Review*

# Recent Major Transcriptomics and Epitranscriptomics Contributions toward Personalized and Precision Medicine

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**Abstract:** With the advent of genome-wide screening methods—beginning with microarray technologies and moving onto next generation sequencing methods—the era of precision and personalized medicine was born. Genomics led the way, and its contributions are well recognized. However, "other-omics" fields have rapidly emerged and are becoming as important toward defining disease causes and exploring therapeutic benefits. In this review, we focus on the impacts of transcriptomics, and its extension—epitranscriptomics—on personalized and precision medicine efforts. There has been an explosion of transcriptomic studies particularly in the last decade, along with a growing number of recent epitranscriptomic studies in several disease areas. Here, we summarize and overview major efforts for cancer, cardiovascular disease, and neurodevelopmental disorders (including autism spectrum disorder and intellectual disability) for transcriptomics/epitranscriptomics in precision and personalized medicine. We show that leading advances are being made in both diagnostics, and in investigative and landscaping disease pathophysiological studies. As transcriptomics/epitranscriptomics screens become more widespread, it is certain that they will yield vital and transformative precision and personalized medicine contributions in ways that will significantly further genomics gains.

**Keywords:** precision medicine; personalized medicine; cancer; cardiovascular disease; neurodevelopmental disorders; intellectual disability; autism spectrum disorder; transcriptomics; epitranscriptomics



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## 1. Introduction

Since microarray technology heralded the advent of the third era in medical diagnostics in the early "noughties", clinical medical genetics has focused on genome-wide screens rather than targeted approaches. Shortly after chromosomal microarray analysis (CMA) was accepted and widely adopted as a first-tier diagnostic test in medical genetics [1], next generation sequencing (NGS) technologies exploded onto the scene. Indeed, the past decade has seen an acceleration in the development and implementation of a plethora of NGS based genomics screens that are ever-decreasing in cost, ever-increasing in diagnostic and clinical utility, and therefore, unsurprisingly, undergoing rapid expansion in utilization by diagnostic laboratories. The most common NGS screens involve interrogating the DNA sequence of the protein coding portion of the genome, termed whole exome sequencing (WES), followed by interrogating the entire whole genome, termed whole genome sequencing (WGS). These techniques and their reach in medical diagnostics have been extensively reported on and reviewed [2–8].

The latter half of the past decade, however, has given us a wide range of NGS-based screening methods other than WES and WGS. The variety and frequency of publication on the plethora of such "omics" approaches admittedly have even caused amusement as scientists and health care providers grapple to keep abreast of them. Indeed, tropes such as "other-omics" or "everything-omics" have commanded some popularity in various media [9]. Nevertheless, some of these "other-omics" have come into their own as

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*Article*

# Decreased Plasma Level of Cytokeratin 20 (KRT20) Is Indicative of the Emergence and Severity of Acute GvHD Irrespective to the Type of Organ Involvement

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**Abstract:** Accurate risk prediction of acute graft versus host disease (aGvHD) is currently an unmet clinical need. This study sought to analyze whether three plasma proteins expressed in a largely skin- and gut-restricted manner would be affected by the development of acute cutaneous and gastrointestinal aGvHD. The diagnostic sensitivity, specificity, and prognostic value of plasma cytokeratin-15 (KRT15) cytokeratin-20 (KRT20), and occludin (OCLN) were evaluated in a discovery and a validation cohort using ELISA in comparison with elafin (PI3) and regenerating family member 3 alpha (REG3A), two established markers of skin- and gut aGvHD. The discovery cohort ($n$ = 39) revealed that at the time of diagnosis, plasma KRT20 showed a progressive decrease from unaffected individuals to patients with single-, and patients with multi-organ aGvHD. KRT20 was affected by cutaneous ($p$ = 0.0263) and gastrointestinal aGvHD ($p$ = 0.0242) independently and in an additive manner. Sensitivity and specificity of KRT20 for aGvHD involving both target organs (AUC = 0.852) were comparable to that of PI3 for skin-aGvHD (AUC = 0.708) or that of REG3A for gut-aGvHD (AUC = 0.855). Patient follow-up in the validation cohort ($n$ = 67) corroborated these observations ($p < 0.001$), and linked low KRT20 to grade 2+ disease ($p < 0.001$), but failed to confirm low KRT20 as an independent risk factor. These data established a link between low plasma KRT20 levels and moderate to severe aGvHD involving multiple target organs.

**Keywords:** acute graft versus host disease; aGvHD; biomarker; cytokeratin 20; KRT20; K20

## 1. Introduction

Despite significant advances in prophylaxis and therapy, acute graft versus host disease (aGvHD) remains one of the most common and life-threatening complications of allogeneic hematopoietic stem cell transplantation (aHSCT) [1]. Acute GvHD develops on

# Genetic predisposition to cancer across people of different ancestries in Qatar: a population-based, cohort study

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## Summary

**Background** Disparities in the genetic risk of cancer among various ancestry groups and populations remain poorly defined. This challenge is even more acute for Middle Eastern populations, where the paucity of genomic data could affect the clinical potential of cancer genetic risk profiling. We used data from the phase 1 cohort of the Qatar Genome Programme to investigate genetic variation in cancer-susceptibility genes in the Qatari population.

**Methods** The Qatar Genome Programme generated high-coverage genome sequencing on DNA samples collected from 6142 native Qataris, stratified into six distinct ancestry groups: general Arab, Persian, Arabian Peninsula, Admixture Arab, African, and South Asian. In this population-based, cohort study, we evaluated the performance of polygenic risk scores for the most common cancers in Qatar (breast, prostate, and colorectal cancers). Polygenic risk scores were trained in The Cancer Genome Atlas (TCGA) dataset, and their distributions were subsequently applied to the six different genetic ancestry groups of the Qatari population. Rare deleterious variants within 1218 cancer susceptibility genes were analysed, and their clinical pathogenicity was assessed by ClinVar and the CharGer computational tools.

**Findings** The cohort included in this study was recruited by the Qatar Biobank between Dec 11, 2012, and June 9, 2016. The initial dataset comprised 6218 cohort participants, and whole genome sequencing quality control filtering led to a final dataset of 6142 samples. Polygenic risk score analyses of the most common cancers in Qatar showed significant differences between the six ancestry groups ($p<0·0001$). Qataris with Arabian Peninsula ancestry showed the lowest polygenic risk score mean for colorectal cancer (–0·41), and those of African ancestry showed the highest average for prostate cancer (0·85). Cancer-gene rare variant analysis identified 76 Qataris (1·2% of 6142 individuals in the Qatar Genome Programme cohort) carrying ClinVar pathogenic or likely pathogenic variants in clinically actionable cancer genes. Variant analysis using CharGer identified 195 individuals carriers (3·17% of the cohort). Breast cancer pathogenic variants were over-represented in Qataris of Persian origin (22 [56·4%] of 39 *BRCA1/BRCA2* variant carriers) and completely absent in those of Arabian Peninsula origin.

**Interpretation** We observed a high degree of heterogeneity for cancer predisposition genes and polygenic risk scores across ancestries in this population from Qatar. Stratification systems could be considered for the implementation of national cancer preventive medicine programmes.

**Funding** Qatar Foundation.



## Introduction

The risk of developing cancer varies according to race, ethnicity, or ancestry.[1] Countries in the Middle East have been experiencing an alarming increase in cancer rates in the past decade.[2] In Qatar, cancer is the nation's second most prevalent non-communicable disease, and the prevalence is projected to increase because of a combination of ageing and population growth.[3] Numerous disease-associated gene variants, including those related to cancer, show substantial diversity in ancestral and derived allele frequencies among different populations. However, disparities in the genetic risk of cancer between ancestry groups remain poorly defined. To our knowledge, Arabian populations, despite their diversity, have not been included in international genome or cancer consortia. The population structure of Arabs might result in the emergence of founder variants that could influence the development or progression of cancer.[4]

Next-generation DNA sequencing is increasingly being considered as a core component of precision medicine because of its rapid developments and because of the potential of whole genome and exome sequencing in predicting genetic predisposition to many diseases.[5] As decreasing costs make next-generation sequencing increasingly affordable, the search for germline variations in cancer susceptibility genes will move from single-gene approaches to genome-wide analyses. Consequently, the targeted population will expand from at-risk individuals of families with cancer to individuals from the general population.

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SHORT COMMUNICATION

WILEY

# Transcriptomic profile investigations highlight a putative role for NUDT16 in sepsis

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## Abstract

Sepsis is an aberrant systemic inflammatory response mediated by the acute activation of the innate immune system. Neutrophils are important contributors to the innate immune response that controls the infection, but harbour the risk of collateral tissue damage such as thrombosis and organ dysfunction. A better understanding of the modulations of cellular processes in neutrophils and other blood cells during sepsis is needed and can be initiated via transcriptomic profile investigations. To that point, the growing repertoire of publicly accessible transcriptomic datasets serves as a valuable resource for discovering and/or assessing the robustness of biomarkers. We employed systematic literature mining, reductionist approach to gene expression profile and empirical *in vitro* work to highlight the role of a Nudix hydrolase family member, NUDT16, in sepsis. The relevance and implication of the expression of NUDT16 under septic conditions and the putative functional roles of this enzyme are discussed.

**KEYWORDS**
ADP-ribosylation, gene expression, mRNA decapping, nudix hydrolase, nudix hydrolase 16 (NUDT16), reductionist approach, sepsis

## 1 | INTRODUCTION

Sepsis is an aberrant systemic inflammatory response mediated by the acute activation of the innate immune system.[1] The disease currently affects 19 million patients worldwide, with the mortality rate between 25% and 30%.[2] Sepsis can clinically deteriorate into shock with the appearance of organ dysfunction and refractory hypotension. During sepsis, the innate immune system is activated by the recognition of pathogen-derived molecules via receptors expressed on a wide range of host cells. Receptor activation causes the release of soluble inflammatory mediators, and microbicidal molecules. Neutrophils are important contributors to the innate immune response that controls infections but can also lead to considerable collateral tissue damage,[3] such as neutrophil extracellular traps

**Abbreviations:** ADP, adenosine diphosphate; DCP1, mRNA-decapping enzymes; GEO, Gene Expression Omnibus; GXB, Gene Expression Browser; IL-6, interleukin 6; LPS, lipopolysaccharide; NETs, Neutrophil extracellular traps; PGN, peptidoglycan; TNFα, tumour necrosis factor alpha.

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# Metabolic and physiologic magnetic resonance imaging in distinguishing true progression from pseudoprogression in patients with glioblastoma

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## Abstract

Pseudoprogression (PsP) refers to treatment-related clinico-radiologic changes mimicking true progression (TP) that occurs in patients with glioblastoma (GBM), predominantly within the first 6 months after the completion of surgery and concurrent chemoradiation therapy (CCRT) with temozolomide. Accurate differentiation of TP from PsP is essential for making informed decisions on appropriate therapeutic intervention as well as for prognostication of these patients. Conventional neuroimaging findings are often equivocal in distinguishing between TP and PsP and present a considerable diagnostic dilemma to oncologists and radiologists. These

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Journal of Translational Medicine

REVIEW Open Access

# Microbiota medicine: towards clinical revolution

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**Abstract**

The human gastrointestinal tract is inhabited by the largest microbial community within the human body consisting of trillions of microbes called gut microbiota. The normal flora is the site of many physiological functions such as enhancing the host immunity, participating in the nutrient absorption and protecting the body against pathogenic microorganisms. Numerous investigations showed a bidirectional interplay between gut microbiota and many organs within the human body such as the intestines, the lungs, the brain, and the skin. Large body of evidence demonstrated, more than a decade ago, that the gut microbial alteration is a key factor in the pathogenesis of many local and systemic disorders. In this regard, a deep understanding of the mechanisms involved in the gut microbial symbiosis/dysbiosis is crucial for the clinical and health field. We review the most recent studies on the involvement of gut microbiota in the pathogenesis of many diseases. We also elaborate the different strategies used to manipulate the gut microbiota in the prevention and treatment of disorders. The future of medicine is strongly related to the quality of our microbiota. Targeting microbiota dysbiosis will be a huge challenge.

**Keywords:** Dysbiosis, Built environment microbiome, Metabolites, miRNAs, Fecal microbiota transplant, Prebiotics, Probiotics, Oral microbiota, Metabolic syndrome

## Background

Microbial medicine has evolved thanks to the tremendous improvement in the understanding of genomics, metagenomics, and metabolomics in the recent years. In light of these advances, modulation of the host microbiome has been proposed as a potential treatment or prophylaxis for many health disorders. In fact, the human body harbors a huge array of microorganisms, among which bacteria have a great role. Other microbes also inhabit our bodies such as viruses, parasites, and fungi [1]. Together, these microbial communities form the human microbiota found in many areas within the human body, such as the skin, the upper airways, the gut, and the genital tracts [2]. The gut saprophytic commensal flora plays a fundamental role in the modulation of several local functions including nutrient absorption [3], the regulation of host immune system [4] and the defense against pathogenic microorganisms [5]. The gut microbiota is very diverse and its density changes along the gastrointestinal tract. However, its diversity is easily altered by different exo- and endogenous factors such as drugs, diet, health status, hygiene and surrounding environmental microorganisms [6]. Alterations in the symbiotic relationship between the microbiota and the enteric microenvironment, comprising cells of the innate and acquired immune system and enteric neurons, underlay

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# Familial long-read sequencing increases yield of *de novo* mutations

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## Summary

Studies of *de novo* mutation (DNM) have typically excluded some of the most repetitive and complex regions of the genome because these regions cannot be unambiguously mapped with short-read sequencing data. To better understand the genome-wide pattern of DNM, we generated long-read sequence data from an autism parent-child quad with an affected female where no pathogenic variant had been discovered in short-read Illumina sequence data. We deeply sequenced all four individuals by using three sequencing platforms (Illumina, Oxford Nanopore, and Pacific Biosciences) and three complementary technologies (Strand-seq, optical mapping, and 10X Genomics). Using long-read sequencing, we initially discovered and validated 171 DNMs across two children—a 20% increase in the number of *de novo* single-nucleotide variants (SNVs) and indels when compared to short-read callsets. The number of DNMs further increased by 5% when considering a more complete human reference (T2T-CHM13) because of the recovery of events in regions absent from GRCh38 (e.g., three DNMs in heterochromatic satellites). In total, we validated 195 *de novo* germline mutations and 23 potential post-zygotic mosaic mutations across both children; the overall true substitution rate based on this integrated callset is at least $1.41 \times 10^{-8}$ substitutions per nucleotide per generation. We also identified six *de novo* insertions and deletions in tandem repeats, two of which represent structural variants. We demonstrate that long-read sequencing and assembly, especially when combined with a more complete reference genome, increases the number of DNMs by >25% compared to previous studies, providing a more complete catalog of DNM compared to short-read data alone.

## Introduction

*De novo* mutations (DNMs) are spontaneous germline mutations that arise through a myriad of mechanisms, such as replication error, DNA damage repair, and non-allelic homologous recombination. Different mechanisms give rise to different types of mutations, the most common of which are small single-base substitutions (single-nucleotide variants [SNVs]) and insertions and deletions of a small number of bases (indels); *de novo* SNVs and indels have been reported at an average rate of approximately 70 DNMs per individual.[1–3] Other classes of mutation, such as expansions of tandem repeats, have been estimated to be very common as well (>50 events per individual) but are currently incompletely ascertained.[4] Larger mutations, such as structural variants (SVs), which affect more than 50 bp, are significantly rarer and have been observed at a rate of approximately one in every six individuals.[5,6] All three classes of mutations have been implicated in autism, and it is estimated that more than 30% of all autism spectrum disorder (ASD) cases may arise as a result of DNM in a protein-coding sequence or a *de novo* SV.[7] These estimates are based almost solely on the analysis of thousands of families via short-read whole-genome sequencing (WGS) datasets. Because long-read WGS methods have greatly increased sensitivity for SVs and large indels as well as all variant classes in repetitive loci,[8,9] we expect *de novo* rates may have been systematically underestimated.

Mapping Illumina sequence data can successfully access approximately 84% of the genome.[10] Repetitive regions, where the same 150 bp long read maps to multiple locations, are typically excluded, potentially underestimating the true mutation rate.[11] In addition, Illumina sequencing is insensitive to large SVs where it is estimated that 75% of events (especially insertions) are missed in callsets generated from short-read sequencing technology.[8] Previous efforts to identify *de novo* variation with long-read

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REVIEW ARTICLE OPEN

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# Genetics of glutamate and its receptors in autism spectrum disorder

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Autism spectrum disorder (ASD) is a neurodevelopmental impairment characterized by deficits in social interaction skills, impaired communication, and repetitive and restricted behaviors that are thought to be due to altered neurotransmission processes. The amino acid glutamate is an essential excitatory neurotransmitter in the human brain that regulates cognitive functions such as learning and memory, which are usually impaired in ASD. Over the last several years, increasing evidence from genetics, neuroimaging, protein expression, and animal model studies supporting the notion of altered glutamate metabolism has heightened the interest in evaluating glutamatergic dysfunction in ASD. Numerous pharmacological, behavioral, and imaging studies have demonstrated the imbalance in excitatory and inhibitory neurotransmitters, thus revealing the involvement of the glutamatergic system in ASD pathology. Here, we review the effects of genetic alterations on glutamate and its receptors in ASD and the role of non-invasive imaging modalities in detecting these changes. We also highlight the potential therapeutic targets associated with impaired glutamatergic pathways.

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## INTRODUCTION

Autism spectrum disorder (ASD) comprises a broad range of conditions, including social, verbal, and repetitive behaviors with intellectual disability (ID). The cost of autism to society is increasing worldwide and is now $126 billion per year in the USA, more than three times the cost in 2006 [1]. Although the etiology of ASD is largely unknown, a broad scientific consensus points to genetics and environmental factors as predisposing characteristics in the development of autistic features.

Evidence from genetic and molecular studies delineates the impairment of synaptic function in ASD, with genes regulating synaptic functions being altered or mutated in ASD [2]. Individuals with ASD show alterations in brain development; however, the mechanism underlying the changes is unknown. The onset of ASD symptoms coincides with the timing of synapse formation and maturation, thus supporting the involvement of synaptic connections and neuronal function in ASD pathogenesis [3]. The arrested synaptic development in autism has been confirmed in human and animal studies, which found an abundance of thin, disrupted, and immature dendritic spines in different forms of ASD. Genes regulating synaptic structure and function are also highly mutated in ASD. The disrupted synaptic function in ASD relates to higher-level phenotypic changes as observed in other neurologic disorders and may result in altered sensory processing, cognitive deficits, hyperactivity, and seizures by affecting the balance between excitatory and inhibitory neurotransmission [4].

The abrupt synaptic connectivity relates to the alterations in glutamate receptor expression and function, subsequently modulating neuronal function [5]. The amino acid glutamate is the most abundant excitatory neurotransmitter in vertebrates and plays a significant role in neuronal development and cognition through its receptors. Defects in glutamate signaling are implicated in autism, but how such defects affect neuronal signal processing and cause varied autistic phenotypes remains unknown [6]. This review article describes how genetic changes affect glutamate and its receptors in ASD and highlights the role of non-invasive imaging modalities in detecting these changes.

### Glutamate receptors

Glutamate is an important excitatory neurotransmitter in the human brain. Glutamate receptors are implicated in various cognitive and neuronal developmental processes such as learning, memory formation, spine maturation, circuit development, and synaptic plasticity [7]. They are categorized as either ionotropic glutamate receptors (iGluRs) or metabotropic glutamate receptors (mGluRs).

The iGluRs are non-selective ion channels induced by glutamate and usher synaptic transmissions throughout the central nervous system [8]. These channels are subcategorized

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Molecular Cancer

REVIEW Open Access

# Liquid biopsy: a step closer to transform diagnosis, prognosis and future of cancer treatments

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**Abstract**

Over the past decade, invasive techniques for diagnosing and monitoring cancers are slowly being replaced by non-invasive methods such as liquid biopsy. Liquid biopsies have drastically revolutionized the field of clinical oncology, offering ease in tumor sampling, continuous monitoring by repeated sampling, devising personalized therapeutic regimens, and screening for therapeutic resistance. Liquid biopsies consist of isolating tumor-derived entities like circulating tumor cells, circulating tumor DNA, tumor extracellular vesicles, etc., present in the body fluids of patients with cancer, followed by an analysis of genomic and proteomic data contained within them. Methods for isolation and analysis of liquid biopsies have rapidly evolved over the past few years as described in the review, thus providing greater details about tumor characteristics such as tumor progression, tumor staging, heterogeneity, gene mutations, and clonal evolution, etc. Liquid biopsies from cancer patients have opened up newer avenues in detection and continuous monitoring, treatment based on precision medicine, and screening of markers for therapeutic resistance. Though the technology of liquid biopsies is still evolving, its non-invasive nature promises to open new eras in clinical oncology. The purpose of this review is to provide an overview of the current methodologies involved in liquid biopsies and their application in isolating tumor markers for detection, prognosis, and monitoring cancer treatment outcomes.

**Keywords:** Liquid biopsy, Cancer, Circulating tumor cells, Circulating tumor DNA, Tumor extracellular vesicles, Non-invasive tumor detection, Precision medicine Cancer diagnosis

## Introduction

Molecular profiling of tumors obtained from individual patients has in recent years been shown to improve the selection of personalized cancer treatment therapies, patient responses, detection of drug resistance, and monitoring of tumor relapse [1, 2]. The standard method of profiling tumors initially involves obtaining resected tumor samples by invasive surgeries. The limitations to such invasive procedures include difficulty in acquiring tumor samples for both tumor quantity and quality (Fig. 1). Moreover, acquiring biopsy samples by invasive methods throughout treatment to monitor tumor response and relapse also poses a major challenge in tumor profiling [3]. Heterogeneity of resected tumor samples as a whole, also limits the use of invasive

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# A 3D transcriptomics atlas of the mouse nose sheds light on the anatomical logic of smell

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AUTHOR CONTRIBUTIONS

M.L.R.T.S. analyzed data and wrote the initial version of the manuscript. E.A.M. performed the RNA-seq experiments and analyzed data. T.S.N., L.S.M., L.W., and S.L. performed experiments. M.M., S.S.Y.H., J.D.M., F.V., M.C., and M.O. analyzed data. E.G., J.R., D.W.L., and B.M. analyzed data and helped write the manuscript. A.S. and L.R.S. conceived and supervised the project, analyzed data, and wrote the final version of the manuscript.

SUPPLEMENTAL INFORMATION

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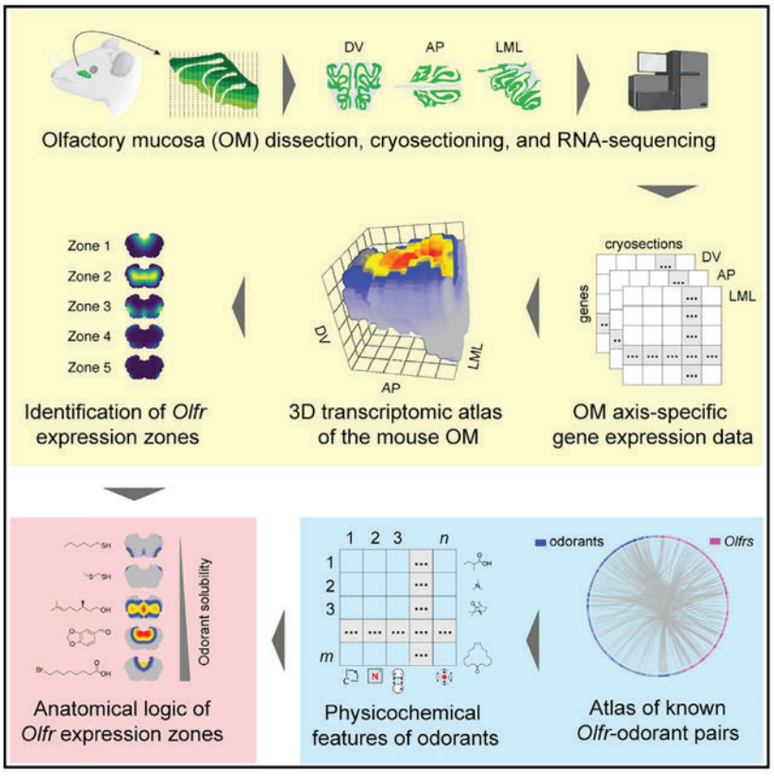
DECLARATION OF INTERESTS

The authors declare no competing interests.

## SUMMARY

The sense of smell helps us navigate the environment, but its molecular architecture and underlying logic remain understudied. The spatial location of odorant receptor genes (*Olfrs*) in the nose is thought to be independent of the structural diversity of the odorants they detect. Using spatial transcriptomics, we create a genome-wide 3D atlas of the mouse olfactory mucosa (OM). Topographic maps of genes differentially expressed in space reveal that both *Olfrs* and non-*Olfrs* are distributed in a continuous and overlapping fashion over at least five broad zones in the OM. The spatial locations of *Olfrs* correlate with the mucus solubility of the odorants they recognize, providing direct evidence for the chromatographic theory of olfaction. This resource resolves the molecular architecture of the mouse OM and will inform future studies on mechanisms underlying *Olfr* gene choice, axonal pathfinding, patterning of the nervous system, and basic logic for the peripheral representation of smell.


## Graphical Abstract




## In brief

Ruiz Tejada Segura et al. employ a spatial transcriptomics approach to create a 3D map of gene expression of the mouse nose and combine it with single-cell RNA-seq, machine learning, and chemoinformatics to resolve its molecular architecture and shed light into the anatomical logic of smell.

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Original Article

# Analysis of incidental findings in Qatar genome participants reveals novel functional variants in *LMNA* and *DSP*

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## Abstract

In order to report clinically actionable incidental findings in genetic testing, the American College of Medical Genetics and Genomics (ACMG) recommended the evaluation of variants in 59 genes associated with highly penetrant mutations. However, there is a lack of epidemiological data on medically actionable rare variants in these genes in Arab populations. We used whole genome sequencing data from 6045 participants from the Qatar Genome Programme and integrated it with phenotypic data collected by the Qatar Biobank. We identified novel putative pathogenic variants in the 59 ACMG genes by filtering previously unrecorded variants based on computational prediction of pathogenicity, variant rarity and segregation evidence. We assessed the phenotypic associations of candidate variants in genes linked to cardiovascular diseases. Finally, we used a zebrafish knockdown and synthetic human mRNA co-injection assay to functionally characterize two of these novel variants. We assessed the zebrafish cardiac function in terms of heart rate, rhythm and hemodynamics, as well as the heart structure. We identified 52 492 novel variants, which have not been reported in global and disease-specific databases. A total of 74 novel variants were selected with potentially pathogenic effect. We prioritized two novel cardiovascular variants, *DSP* c.1841A > G (p.Asp614Gly) and *LMNA* c.326 T > G (p.Val109Gly) for functional characterization. Our results showed that both variants resulted in abnormal zebrafish heart rate, rhythm and structure. This study highlights medically actionable variants that are specific to the Middle Eastern Qatari population.

## Introduction

The American College of Medical Genetics and Genomics (ACMG) recommends reporting medically actionable pathogenic variants in 59 genes when ordering clinical genomic testing (1,2). Individuals carrying pathogenic variants in these 59 genes are at high risk to develop highly penetrant diseases in the future. Early detection and screening can be beneficial for them to receive early medical intervention and ameliorate the clinical presentation. The frequency of these medically actionable variants had been assessed in global population studies (3–7). However, there is a lack of data on the frequency of medically actionable variants in ethnic groups that are not well represented in global sequencing efforts, such as the Middle Eastern population. Moreover, the frequency of rare medically actionable variants in the Qatari population is predicted to be high due to the founder effect and high consanguinity rate in Qatar (8–12). The WGS and comprehensive phenotypic data collected by the Qatar Genome Programme (QGP) and the Qatar Biobank (QBB) allows us to investigate the prevalence of medically actionable variants in the Qatari population and to identify novel, potentially pathogenic variants in clinically relevant genes.

In this study, we analyzed the novel variants in the 59 ACMG genes using 6045 WGS data from the pilot phase of the QGP. These variants were not reported previously in any database. We assessed the clinical phenotypic data associated with cardiovascular diseases for the genotype positive QGP participants in order to identify putative novel variants that could cause cardiovascular diseases.

Zebrafish is a very useful *in vivo* cardiac disease model to characterize the pathogenicity of predicted

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# Anticancer activity of Neosetophomone B by targeting AKT/SKP2/MTH1 axis in leukemic cells

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ABSTRACT

Neosetophomone B (NSP–B), a meroterpenoid fungal secondary metabolite, was investigated for its anticancer potential in leukemic cell lines (K562 and U937). NSP-B treatment of leukemic cells suppressed cell viability by triggering apoptotic cell death. Apoptosis induced by NSP-B is triggered by mitochondrial signaling and caspase activation. Additionally, NSP-B treatment of leukemic cells causes AKT's inactivation accompanied by downregulation of SKP2 oncogene and MTH1 with a concomitant increase of p21Cip1and p27Kip1. Furthermore, NSP-B causes suppression of antiapoptotic proteins, including cIAP1, cIAP2, XIAP, survivin and BCl-XL. Overall, NSP-B reduces cell viability by mitochondrial and caspase-dependent apoptosis. The inhibition of AKT and SKP2 axis could be a promising therapeutic target for leukemia treatment.



## 1. Introduction

Meroterpenoids are natural products with mixed biosynthetic origins [1]. They are partially derived from terpenoid biosynthetic pathways [2]. They have been isolated from fungi, marine organisms, animals, and plants and display remarkable structural diversity [3]. Meroterpenoids exhibit various biological properties, including anticancer, anti-inflammatory, antioxidant, and antibacterial activities [1]. Their chemical structural diversity and complexity, potential bioactivities, and pharmacological effects make them attractive targets for chemists and pharmacologists [1–3]. Neosetophomone B (NSP–B), a meroterpenoid fungal secondary metabolite, was isolated along with five structurally related ones from an undescribed *Neosetophoma* sp. (strain MSX50044) [4]. The cytotoxic effect of NSP-B at micromolar concentrations has been reported in breast and ovarian cancer cell lines [4]. However, the mechanism of NSP-B mediated cytotoxicity is not known.

The proteasome is a multi-catalytic complex consisting of two major regulators, PA28 and PA700, forming 26S proteasome [5]. The 26 S proteasome is responsible for the degradation of many polypeptides critical for cell death signaling [6]. These include tumor suppressors (p53, p21), cyclins, nuclear factor kappa B (NF-kB), and mitosis-regulating proteins [7,8]. The oncogenic F-box protein, S-phase kinase protein-2 (SKP2), regulates the expression of cell cycle inhibitor protein, p27Kip1, via associating with ubiquitin E3 ligase complex [9,10]. A high level of SKP2 expression with a

*Abbreviations:* NSP-B, Neosetophomone B; SKP2, S-phase kinase protein-2; IAPs, inhibitors of apoptosis proteins; PARP, poly-ADP ribose polymerase.

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# A Novel *FGFR1* Missense Mutation in a Portuguese Family with Congenital Hypogonadotropic Hypogonadism

**Lúcia Fadiga [1,†], Mariana Lavrador [1,†], Nuno Vicente [1], Luísa Barros [1], Catarina I. Gonçalves [2], Asma Al-Naama [3], Luis R. Saraiva [3,*] and Manuel C. Lemos [2,*]**

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**Abstract:** Congenital hypogonadotropic hypogonadism (CHH) is a rare reproductive endocrine disorder characterized by complete or partial failure of pubertal development and infertility due to deficiency of the gonadotropin-releasing hormone (GnRH). CHH has a significant clinical heterogeneity and can be caused by mutations in over 30 genes. The aim of this study was to investigate the genetic defect in two siblings with CHH. A woman with CHH associated with anosmia and her brother with normosmic CHH were investigated by whole exome sequencing. The genetic studies revealed a novel heterozygous missense mutation in the Fibroblast Growth Factor Receptor 1 (*FGFR1)* gene (NM_023110.3: c.242T>C, p.Ile81Thr) in the affected siblings and in their unaffected father. The mutation affected a conserved amino acid within the first Ig-like domain (D1) of the protein, was predicted to be pathogenic by structure and sequence-based prediction methods, and was absent in ethnically matched controls. These were consistent with a critical role for the identified missense mutation in the activity of the FGFR1 protein. In conclusion, our identification of a novel missense mutation of the *FGFR1* gene associated with a variable expression and incomplete penetrance of CHH extends the known mutational spectrum of this gene and may contribute to the understanding of the pathogenesis of CHH.

**Keywords:** hypogonadotropic hypogonadism; Kallmann syndrome; FGFR1; fibroblast growth factor receptor 1; genetics; mutation



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## 1. Introduction

Congenital hypogonadotropic hypogonadism (CHH) is a rare condition characterized by absent or incomplete puberty and infertility due to a deficient production, secretion or action of the gonadotropin-releasing hormone (GnRH) [1,2]. Patients have low serum concentrations of the gonadotropins LH (luteinizing hormone) and FSH (follicle-stimulating hormone) and low concentrations of sex steroids [1,2].

CHH has a significant clinical heterogeneity, and the diagnosis is often difficult to differentiate from constitutional delay of growth and puberty [3]. CHH includes Kallmann Syndrome, which is characterized by GnRH deficiency with a defective sense of smell (i.e., anosmia or hyposmia), and CHH without olfactory defects (normosmic CHH). Non-reproductive phenotypes may also be found in CHH patients, such as midline facial and brain defects, dental agenesis, sensorineural hearing impairment, renal agenesis and skeletal defects [1,2].

There are over 30 genes associated with CHH [4,5]. Although most families reveal a Mendelian inheritance pattern (X-linked, autosomal recessive or autosomal dominant),

Review Article

Nadien AbouHashem, Kholoud Al-Shafai and Mashael Al-Shafai*

# The genetic elucidation of monogenic obesity in the Arab world: a systematic review

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**Abstract**

**Background:** Investigation of monogenic obesity (MO), a rare condition caused by a single gene variant(s), especially in consanguineous populations, is a powerful approach for obtaining novel insights into the genetic alterations involved. Here, we present a systematic review of the genetics of MO in the 22 Arab countries and apply protein modeling *in silico* to the missense variants reported.
**Methods:** We searched four literature databases (PubMed, Web of Science, Science Direct and Scopus) from the time of their first creation until December 2020, utilizing broad search terms to capture all genetic studies related to MO in the Arab countries. Only articles published in peer-reviewed journals involving subjects from at least one of the 22 Arab countries and dealing with genetic variants related to MO were included. Protein modelling of the variants identified was performed using PyMOL.
**Results:** The 30 cases with severe early-onset obesity identified in 13 studies carried 14 variants in five genes (*LEP, LEPR, POMC, MC4R and CPE*). All of these variants were pathogenic, homozygous and carried by members of consanguineous families.
**Conclusion:** Despite the elevated presence of consanguinity in the Arab countries, the genetic origins of MO remain largely unexplained and require additional studies, both of a genetic and functional character.

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**Keywords:** Arabs; childhood obesity; Middle East; monogenic obesity; rare variants.

## Introduction

Childhood obesity is a major global health problem, with more than 340 million cases worldwide in 2017 [1]. In Arab countries, the prevalence of childhood obesity has been increasing dramatically due to the sedentary lifestyle and increased consumption of food rich in fat associated with improvements in living standards [2]. In addition, genetic predisposition exerts a considerable impact on susceptibility to obesity in these countries, as shown by early twin studies and the discovery of rare monogenic forms of obesity [3, 4].

Monogenic obesity (MO) resulting from a single gene variant(s) leads to severe obesity with onset usually before the age of 5 [5, 6]. Many of the genes which predispose for the development of MO encode proteins related to the leptin-melanocortin pathway responsible for food intake and energy expenditure, including leptin (*LEP*), the leptin receptor (*LEPR*), preopiomelanocortin (*POMC*), prohormone convertase 1 (*PCSK1*) and the melanocortin 4 receptor (*MC4R*) [7]. In addition to the new knowledge attained, the discovery of genes and variants that predispose for obesity facilitates clinical diagnosis and management of this disease, as well as the development of pharmacological therapy for certain forms [3, 8].

Studies on consanguineous populations have provided invaluable insights into the genes and variants thereof that are involved in the development of MO, especially those inherited in autosomal recessive fashion. For example, the first MO gene in humans (the *LEP* gene) was identified in consanguineous families from Pakistan [9, 10]. The extensive prevalence of consanguinity in Arab countries, due to sociocultural and religious factors, has motivated investigations of this nature in these countries and, here, we present a systematic review of such reports published to date.

genes

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# In Silico Analysis Identified Putative Pathogenic Missense nsSNPs in Human *SLITRK1* Gene

**Muhammad Zeeshan Ali [1], Arshad Farid [1], Safeer Ahmad [1], Muhammad Muzammal [1], Mohammed Al Mohaini [2,3], Abdulkhaliq J. Alsalman [4], Maitham A. Al Hawaj [5], Yousef N. Alhashem [6], Abdulmonem A. Alsaleh [6], Eman M. Almusalami [7], Mahpara Maryam [8] and Muzammil Ahmad Khan [1,9,*]**

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**Abstract:** Human DNA contains several variations, which can affect the structure and normal functioning of a protein. These variations could be single nucleotide polymorphisms (SNPs) or insertion-deletions (InDels). SNPs, as opposed to InDels, are more commonly present in DNA and may cause genetic disorders. In the current study, several bioinformatic tools were used to prioritize the pathogenic variants in the *SLITRK1* gene. Out of all of the variants, 16 were commonly predicted to be pathogenic by these tools. All the variants had very low frequency, i.e., <0.0001 in the global population. The secondary structure of all filtered variants was predicted, but no structural change was observed at the site of variation in any variant. Protein stability analysis of these variants was then performed, which determined a decrease in protein stability of 10 of the variants. Amino acid conservation analysis revealed that all the amino acids were highly conserved, indicating their structural and functional importance. Protein 3D structure of wildtype SLITRK1 and all of its variants was predicted using I-TASSER, and the effect of variation on 3D structure of the protein was observed using the Missense3D tool, which presented the probable structural loss in three variants, i.e., Asn529Lys, Leu496Pro and Leu94Phe. The wildtype SLITRK1 protein and these three variants were independently docked with their close interactor protein PTPRD, and remarkable differences were observed in the docking sites of normal and variants, which will ultimately affect the functional activity of the SLITRK1 protein. Previous studies have shown that mutations in *SLITRK1* are involved in Tourette syndrome. The present study may assist a molecular geneticist in interpreting the variant pathogenicity in research as well as diagnostic setup.

**Keywords:** *SLITRK1*; bioinformatical tools; pathogenic; docking

## 1. Introduction

Human DNA contains several variations in its sequence including single nucleotide polymorphisms (SNPs) and insertion deletions (InDels). However, SNPs are the most

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# In Silico Analysis of the L-2-Hydroxyglutarate Dehydrogenase Gene Mutations and Their Biological Impact on Disease Etiology

**Muhammad Muzammal [1], Alessandro Di Cerbo [2,*], Eman M. Almusalami [3], Arshad Farid [1,*], Muzammil Ahmad Khan [1,4], Shakira Ghazanfar [5], Mohammed Al Mohaini [6,7], Abdulkhaliq J. Alsalman [8], Yousef N. Alhashem [9], Maitham A. Al Hawaj [10] and Abdulmonem A. Alsaleh [9]**

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**Abstract:** The L-2-hydroxyglutarate dehydrogenase (L2HGDH) gene encodes an important mitochondrial enzyme. However, its altered activity results in excessive levels of L-2-hydroxyglutarate, which results in diverse psychiatric features of intellectual disability. In the current study, we executed an in-silico analysis of all reported L2HGDH missense and nonsense variants in order to investigate their biological significance. Among the superimposed 3D models, the highest similarity index for a wild-type structure was shown by the mutant Glu336Lys (87.26%), while the lowest similarity index value was shown by Arg70* (10.00%). Three large active site pockets were determined using protein active site prediction, in which the 2nd largest pocket was shown to encompass the substrate L-2-hydroxyglutarate (L2HG) binding residues, i.e., 89Gln, 195Tyr, 402Ala, 403Gly and 404Val. Moreover, interactions of wild-type and mutant L2HGDH variants with the close functional interactor D2HGDH protein resulted in alterations in the position, number and nature of networking residues. We observed that the binding of L2HG with the L2HGDH enzyme is affected by the nature of the amino acid substitution, as well as the number and nature of bonds between the substrate and protein molecule, which are able to affect its biological activity.

**Keywords:** L2HGDH; metabolism; in silico analysis; modeling and docking



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## 1. Introduction

L-2-hydroxyglutaric aciduria (L2HGA, OMIM #236792) is a very rare genetic condition of the metabolism. It occurs due to null or reduced action of L-2-hydroxyglutarate dehydrogenase (L2HGDH), a mitochondrial enzyme that catalyzes the oxidation of L-2-hydroxyglutaric acid into α-ketoglutarate [1–3]. L2HGDH is encoded by the L2HGDH gene and is an autosomal recessive condition that occurs due to an increased level of L-2-hydroxyglutaric acid in the urine, plasma and cerebrospinal fluid (CSF) [1].

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ORIGINAL RESEARCH
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# Increased Relative Abundance of *Ruminoccocus* Is Associated With Reduced Cardiovascular Risk in an Obese Population

*Arun Prasath Lakshmanan*[1], *Sara Al Zaidan*[1], *Dhinoth Kumar Bangarusamy*[1], *Sahar Al-Shamari*[2], *Wahiba Elhag*[2] *and Annalisa Terranegra*[1]*

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**Background:** Obesity is a complex disease with underlying genetic, environmental, psychological, physiological, medical, and epigenetic factors. Obesity can cause various disorders, including cardiovascular diseases (CVDs), that are among the most prevalent chronic conditions in Qatar. Recent studies have highlighted the significant roles of the gut microbiome in improving the pathology of various diseases, including obesity. Thus, in this study, we aimed to investigate the effects of dietary intake and gut microbial composition in modulating the risk of CVD development in obese Qatari adults.

**Methods:** We enrolled 46 adult subjects (18–65 years of age) who were classified based on their CVD risk scores, calculated using the Framingham formula, into a CVD no-risk group (score of $<$10%, $n = 36$) and CVD risk group (score of $\geq$10%, $n = 10$). For each study subject, we measured the gut microbial composition with a 16s rDNA sequencing method that targeted the v3-v4 region using Illumina Miseq, and their nutritional status was recorded based on 24-h dietary recall. Dietary intake, bacterial taxa summary, diversity index, microbial markers, pathway analysis, and network correlation were determined for the study subjects.

**Results:** The CVD risk group showed a lower intake of vitamin D, reduced relative abundance of genera *Ruminococcus* and *Bifidobacterium*, no change in bacterial diversity, and higher levels of taurine, hypotaurine, and lipoic acid metabolism than the CVD no-risk group. Besides, the relative abundance of genus *Ruminococcus* was positively correlated with the intake of protein, monounsaturated fat, vitamin A, and vitamin D.

**Conclusion:** Taken together, our results suggest that the genus *Ruminococcus* could be used as a microbial marker, and its reduced relative abundance could mediate the risk of CVDs in the Obese Qatari population.

**Keywords: *Ruminococcus*, CVD risk, obesity, vitamin D, diet**

# Expression Pattern and Prognostic Significance of Chemokines in Breast cancer: An Integrated Bioinformatics Analysis

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## Abstract

**Chemokines, low molecular weight cytokines are central to the trafficking of immune cells, stromal modulation, and inflammation. Recent studies have demonstrated an intricate connection between chemokines and tumor metastasis. In the present study, we evaluated the expression pattern and prognostic significance of chemokines in BC and found significant deregulation in chemokine expression. Also, the chemokine expression pattern was associated with the prognosis of BC patients. Enrichment analysis and functional analysis revealed the involvement of chemokines in BC tumorigenicity via NFkB and TLR pathways. High deregulation of chemokines in BC points towards their involvement in BC tumorigenesis and may prove as novel therapeutic targets to treat metastatic BC.**

**Background:** Breast cancer (BC), one of the most prevalent malignancies, is the second major cause of mortality from cancer among women worldwide. Even though substantial progress has been made in breast cancer treatment, metastasis still accounts for the majority of the deaths. The tumor microenvironment (TME) comprising stromal and non-stromal components is central to tumor growth and development and is partly regulated by chemokines. Chemokines regulate immune cell trafficking, the development of stroma and play a key role in inflammation, a cancer hallmark. **Methods:** In the present study, we used a bioinformatics approach to identify highly deregulated chemokines in BC patients. We performed expression analysis, survival analysis, gene ontology analysis, KEGG analysis, and protein-protein interaction network analysis of the deregulated chemokines using Gepia2, UALCAN, Kaplan-Meier Plotter, DAVID, and STRING tools. **Results:** We identified >2-fold change (FC) increase in CXCL9/10/11/13 and >-2 FC decrease in CCL14/21/28, CXCL2/12 CX3CL1. Also, increased expression of CCL14, CCL21, CXCL13, CXCL9, CXCL12 correlated with better overall survival (OS) of BC patients. **Conclusions:** Our results strongly indicate that chemokines may have potential biomarker characteristics, and the constructed PPI network contributed to an in-depth understanding of the chemokine networks. The deregulated chemokines may prove to be therapeutic targets for the effective management of BC.

*Clinical Breast Cancer,* Vol. 22, No. 6, 567–578 

**Keywords:** Gene Ontology, Tumor Microenvironment, Metastasis, Inflammation, Immunomodulation, Protein-Protein Interactions

## Introduction

Presently, breast cancer (BC) is the predominant malignancy with the highest incidence, accounting for up to 30% of new cancer cases diagnosed among women.[1] Recent cancer statistics data reveal that among women, BC is the primary cause of cancer-related deaths.[1,2] The complete etiology of BC has yet to be identified, although this multifactorial disorder is frequently correlated with lifestyle, genetic and environmental influences.[3] BC is a highly heterogeneous disease with distinct subtypes, including low-grade (luminal A, luminal B, HER-2 enriched) and high-grade triple-negative breast cancer (TNBC). BC patients have better survival than other malignan-

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*Article*

# Whole-Genome Sequencing of 100 Genomes Identifies a Distinctive Genetic Susceptibility Profile of Qatari Patients with Hypertension

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**Abstract:** Essential hypertension (EH) is a leading risk condition for cardiovascular and renal complications. While multiple genes are associated with EH, little is known about its genetic etiology. Therefore, this study aimed to screen for variants that are associated with EH in 100 hypertensive/100 control patients comprising Qatari individuals using GWASs of whole-genome sequencing and compare these findings with genetic data obtained from more than 10,000 published peer-reviewed studies on EH. The GWAS analysis performed with 21,096 SNPs revealed 38 SNPs with a significant ≥4 log-*p* value association with EH. The two highest EH-associated SNPs (rs921932379 and rs113688672) revealed a significance score of ≥5 log-*p* value. These SNPs are located within the inter-genic region of *GMPS-SETP14* and *ISCA1P6-AC012451.1*, respectively. Text mining yielded 3748 genes and 3078 SNPs, where 51 genes and 24 SNPs were mentioned in more than 30 and 10 different articles, respectively. Comparing our GWAS results to previously published articles revealed 194 that are unique to our patient cohort; of these, 13 genes that have 26 SNPs are the most significant with ≥4 log-*p* value. Of these genes, *C2orf47-SPATS2L* contains nine EH-associated SNPs. Most of EH-associated genes are related to ion gate channel activity and cardiac conduction. The disease–gene analysis revealed that a large number of EH-associated genes are associated with a variety of cardiovascular disorders. The clustering analysis using EH-associated SNPs across different ethnic groups showed high frequency for the minor allele in different ethnic groups, including Africans, East Asians, and South Asians. The combination of GWAS and text mining helped in identifying the unique genetic susceptibility profile of Qatari patients with EH. To our knowledge, this is the first small study that searched for genetic factors associated with EH in Qatari patients.

**Keywords:** genome-wide association; GWAS; hypertension; genomics; whole-genome sequencing; genomic biomarkers; SNPs; precision medicine; Qatar Biobank; QBB; Qatar



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## 1. Introduction

Cardiovascular disorders cause about 17 million deaths worldwide, with about one-third of these being due to hypertension complications [1]. Essential hypertension (EH) is a chronic and age-related disorder that frequently causes cardiovascular and renal risks. EH affects 25–35% of the adult population in both developed and developing countries, leading to stroke and cardiovascular disorders. Of these, up to 60–70% are in their mid-sixties [2,3]. Several factors, such as the large arteries, endocrine factors, central nervous system, and microcirculation, are involved. The correlation between these factors varies with age and reflects the heterogeneous pattern of hemodynamic changes [2]. A data survey of the global burden of disease showed that in 2015, 7.8 million deaths were related to a systolic blood pressure of ≥140 mmHg, which is the current clinical threshold for identifying hypertension [4].

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# Dendritic cell activation and screening for key molecular signatures required for the induction of allergic responses

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## ABSTRACT

The chain of events that leads to the sensitization of the immune system to environmental antigens, resulting in the onset of allergic disease, has been studied in great detail over the past 30 years. However, during this time, the rate of allergic diseases has increased exponentially, indicating the need to concentrate our studies on host-environmental factors that contribute to the onset of disease. Monocyte-derived dendritic cells (DCs) play a key role in driving localized and systemic immune responses. In this study, we developed a platform for screening the molecular signature and phenotypic profile of DCs activated by allergenic stimuli, including TSLP, IL-25, IL-33, IL-1a, Vit-D3 (1α,25-Dihydroxyvitamin D3), PAR1-AP Peptide, Papain, and recombinant human DerP1 protein to induce a type II associated inflammatory signature. Following activation with allergenic stimuli, modulated DCs are subjected to deep phenotyping via flow cytometry for surface and intracellular markers to detect and/or validate immunomodulatory properties. RNA sequencing is further used to compare the gene expression profiles of DCs responding to either allergenic or microbial stimuli, including the TLR3 agonist dsRNA Poly I:C and TLR4 agonist LPS. In our study, we aimed to identify key molecular signatures of DCs involved in the development of asthma and allergy based on their comparative activation with this broad panel of allergens. We expect to determine central control modules of transcription factors in DCs associated with Th2 induction.

Keywords: allergic response, DC activation, molecular signature

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ORIGINAL ARTICLE

Epidemiology and Genetics

# Comparing the levels of CTLA-4-dependent biological defects in patients with LRBA deficiency and CTLA-4 insufficiency

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## Abstract

**Background:** Lipopolysaccharide-responsive beige-like anchor protein (LRBA) deficiency and cytotoxic T-lymphocyte protein-4 (CTLA-4) insufficiency are recently described disorders that present with susceptibility to infections, autoimmunity, and lymphoproliferation. Clinical and immunological comparisons of the diseases with long-term follow-up have not been previously reported. We sought to compare the clinical and laboratory manifestations of both diseases and investigate the role of flow cytometry in predicting the genetic defect in patients with LRBA deficiency and CTLA-4 insufficiency.

**Methods:** Patients were evaluated clinically with laboratory assessments for lymphocyte subsets, T follicular helper cells ($T_{FH}$), LRBA expression, and expression of CD25, FOXP3, and CTLA4 in regulatory T cells (Tregs) at baseline and 16 h post-stimulation.

**Results:** LRBA-deficient patients ($n = 29$) showed significantly early age of symptom onset, higher rates of pneumonia, autoimmunity, chronic diarrhea, and failure to thrive compared to CTLA-4 insufficiency ($n = 12$). In total, 29 patients received abatacept with favorable responses and the overall survival probability was not different between transplanted versus non-transplanted patients in LRBA deficiency. Meanwhile, higher probability of survival was observed in CTLA-4-insufficient patients ($p = 0.04$). The T-cell subsets showed more deviation to memory cells in CTLA-4-insufficiency, accompanied by low percentages of Treg and dysregulated $cT_{FH}$ cells response in both diseases. Cumulative numbers of autoimmunities positively correlated with $cT_{FH}$ frequencies. Baseline CTLA-4 expression was significantly diminished in LRBA deficiency and CTLA-4 insufficiency, but significant induction in CTLA-4 was observed after short-term T-cell stimulation in LRBA deficiency and controls, while this elevation was less in CTLA-4 insufficiency, allowing to differentiate this disease from LRBA deficiency with high sensitivity (87.5%) and specificity (90%).

**Conclusion:** This cohort provided detailed clinical and laboratory comparisons for LRBA deficiency and CTLA-4 insufficiency. The flow cytometric approach is useful in predicting the defective gene; thus, targeted sequencing can be conducted to provide rapid diagnosis and treatment for these diseases impacting the CTLA-4 pathway.

**KEYWORDS**
CTLA-4, inborn errors of immunity, LRBA, T follicular helper cells, Treg

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# Cross-talk between the microbiome and chronic inflammation in esophageal cancer: potential driver of oncogenesis

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**Abstract**
Esophageal cancer (EC) is frequently considered a lethal malignancy and is often identified at a later stage. It is one of the major causes of cancer-related deaths globally. The conventional treatment methods like chemotherapy, radiotherapy, and surgery offer limited efficacy and poor clinical outcome with a less than 25% 5-year survival rate. The poor prognosis of EC persists despite the growth in the development of diagnostic and therapeutic modalities to treat EC. This underlines the need to elucidate the complex molecular mechanisms that drive esophageal oncogenesis. Apart from the role of the tumor microenvironment and its structural and cellular components in tumorigenesis, mounting evidence points towards the involvement of the esophageal microbiome, inflammation, and their cross-talk in promoting esophageal cancer. The current review summarizes recent research that delineates the underlying molecular mechanisms by which the microbiota and inflammation promote the pathophysiology of esophageal cancer, thus unraveling targets for potential therapeutic intervention.

**Keywords** Esophageal squamous cell carcinoma · Esophageal adenocarcinoma · Inflammation, Microbiome · Tumor microenvironment

## 1 Introduction

Esophageal cancer (EC) is the sixth most common cause of cancer mortality and the eighth-most commonly detected cancer worldwide [1]. Histologically, esophageal squamous cell carcinoma (ESCC) is the most predominant subtype, followed by the esophageal adenocarcinoma (EAC), the latter being increasingly reported in the western nations [2]. In contrast, ESCC is more common in Asia and Africa [3]. ESCC can be found throughout the esophagus, while EAC occurs in the distal region of the esophagus [3]. Risk factors for EAC are markedly different from those of ESCC. Tobacco smoking, genetic factors, excessive consumption of alcohol, intake of red meat, and very hot beverages are common risk factors for ESCC [4–7]. Another potential risk factor is poor oral health due to the shift in the oral microbiome [8–10]. In comparison, the main risk factors for EAC include obesity, gastroesophageal reflux disease (GERD), *Helicobacter pylori* infection (inverse association), and the pattern of sex difference [11].

Environmental exposure can contribute to chronic inflammation and epithelial cell transformation in both the EC subtypes, leading to precancerous lesions and cancerous

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# Odor blocking of stress hormone responses

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**Scents have been employed for millennia to allay stress, but whether or how they might do so is largely unknown. Fear and stress induce increases in blood stress hormones controlled by hypothalamic corticotropin releasing hormone neurons (CRHNs). Here, we report that two common odorants block mouse stress hormone responses to three potent stressors: physical restraint, predator odor, and male–male social confrontation. One odorant inhibits restraint and predator odor activation of excitatory neurons upstream of CRHNs in the bed nucleus of the stria terminalis (BNSTa). In addition, both activate inhibitory neurons upstream of CRHNs in the hypothalamic ventromedial nucleus (VMH) and silencing of VMH inhibitory neurons hinders odor blocking of stress. Together, these findings indicate that odor blocking can occur via two mechanisms: (1) Inhibition of excitatory neurons that transmit stress signals to CRHNs and (2) activation of inhibitory neurons that act directly or indirectly to inhibit stressor activation of CRHNs.**

**Abbreviations**

| | |
|---|---|
| AH | Anterior hypothalamic area |
| ARC | Arcuate hypothalamic nucleus |
| AVPe | Anteroventral periventricular nucleus |
| BNSTa | Bed nucleus of the stria terminalis, anterior part |
| BNSTp | Bed nucleus of the stria terminalis, posterior part |
| DMH | Dorsomedial hypothalamic nucleus |
| LH | Lateral hypothalamic area |
| LPAG | Lateral periaqueductal grey |
| LPGi | Lateral paragigantocellular nucleus |
| LPO | Lateral preoptic area |
| LS | Lateral septal nucleus |
| MnPO | Median preoptic nucleus |
| MPA | Medial preoptic area |
| MPO | Medial preoptic nucleus |
| MTu | Medial tuberal nucleus |
| NTS | Nucleus of the solitary tract |
| PBN | Parabrachial nucleus |
| Pe | Periventricular nucleus of the hypothalamus |
| PH | Posterior hypothalamic nucleus |
| PLH | Peduncular part of lateral hypothalamus |
| PMV | Premammillary nucleus, ventral part |
| SCh | Suprachiasmatic nucleus |
| SHy | Septohippocampal nucleus |
| StHy | Striohypothalamic nucleus |
| VMH | Ventromedial hypothalamic nucleus |
| ZI | Zona incerta |

The mammalian olfactory system detects myriad volatile chemicals perceived as odors as well as animal cues that stimulate innate behavioral or physiological responses[1–3]. The historical use of odors[4] to quell stress suggests

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RESEARCH Open Access

# Discovery of new therapeutic targets in ovarian cancer through identifying significantly non-mutated genes

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## Abstract

**Background:** Mutated and non-mutated genes interact to drive cancer growth and metastasis. While research has focused on understanding the impact of mutated genes on cancer biology, understanding non-mutated genes that are essential to tumor development could lead to new therapeutic strategies. The recent advent of high-throughput whole genome sequencing being applied to many different samples has made it possible to calculate if genes are significantly non-mutated in a specific cancer patient cohort.

**Methods:** We carried out random mutagenesis simulations of the human genome approximating the regions sequenced in the publicly available Cancer Growth Atlas Project for ovarian cancer (TCGA-OV). Simulated mutations were compared to the observed mutations in the TCGA-OV cohort and genes with the largest deviations from simulation were identified. Pathway analysis was performed on the non-mutated genes to better understand their biological function. We then compared gene expression, methylation and copy number distributions of non-mutated and mutated genes in cell lines and patient data from the TCGA-OV project. To directly test if non-mutated genes can affect cell proliferation, we carried out proof-of-concept RNAi silencing experiments of a panel of nine selected non-mutated genes in three ovarian cancer cell lines and one primary ovarian epithelial cell line.

**Results:** We identified a set of genes that were mutated less than expected (non-mutated genes) and mutated more than expected (mutated genes). Pathway analysis revealed that non-mutated genes interact in cancer associated pathways. We found that non-mutated genes are expressed significantly more than mutated genes while also having lower methylation and higher copy number states indicating that they could be functionally important. RNAi silencing of the panel of non-mutated genes resulted in a greater significant reduction of cell viability in the cancer cell lines than in the non-cancer cell line. Finally, as a test case, silencing ANKLE2, a significantly non-mutated gene, affected the morphology, reduced migration, and increased the chemotherapeutic response of SKOV3 cells.

**Conclusion:** We show that we can identify significantly non-mutated genes in a large ovarian cancer cohort that are well-expressed in patient and cell line data and whose RNAi-induced silencing reduces viability in three ovarian cancer cell lines. Targeting non-mutated genes that are important for tumor growth and metastasis is a promising approach to expand cancer therapeutic options.

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BRIEF RESEARCH REPORT
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# Single Extracellular Vesicle Analysis Using Flow Cytometry for Neurological Disorder Biomarkers

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Extracellular vesicles (EVs) are membrane vesicles released from cells to the extracellular space, involved in cell-to-cell communication by the horizontal transfer of biomolecules such as proteins and RNA. Because EVs can cross the blood-brain barrier (BBB), circulating through the bloodstream and reflecting the cell of origin in terms of disease prognosis and severity, the contents of plasma EVs provide non-invasive biomarkers for neurological disorders. However, neuronal EV markers in blood plasma remain unclear. EVs are very heterogeneous in size and contents, thus bulk analyses of heterogeneous plasma EVs using Western blot and ELISA have limited utility. In this study, using flow cytometry to analyze individual neuronal EVs, we show that our plasma EVs isolated by size exclusion chromatography are mainly CD63-positive exosomes of endosomal origin. As a neuronal EV marker, neural cell adhesion molecule (NCAM) is highly enriched in EVs released from induced pluripotent stem cells (iPSCs)-derived cortical neurons and brain organoids. We identified the subpopulations of plasma EVs that contain NCAM using flow cytometry-based individual EV analysis. Our results suggest that plasma NCAM-positive neuronal EVs can be used to discover biomarkers for neurological disorders.

**Keywords: exosome, extracellular vesicle, biomarker, NCAM, neurological disorder**

## INTRODUCTION

Extracellular vesicles (EVs) are lipid bilayer-enclosed vesicles that exist in all body fluids including blood. EVs comprise exosomes and ectosomes, which are distinguished by biogenesis, content, size, release pathways, and function (Kalluri and LeBleu, 2020). Exosomes with the size range of 50–150 nm in diameter originate from the endosomal pathway and are released by the membrane fusion of multivesicular bodies (MVBs) with the plasma membrane, whereas ectosomes ranging from 50 nm to 1 μm in diameter are secreted through the plasma membrane budding (Kalluri and LeBleu, 2020). EVs are secreted from cells and involved in cell–cell communication by the horizontal transfer of the EV contents (Veziroglu and Mias, 2020).

SOFTWARE TOOL ARTICLE

# The third international hackathon for applying insights into large-scale genomic composition to use cases in a wide range of organisms [version 1; peer review: 1 approved, 3 approved with reservations]

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## Abstract

In October 2021, 59 scientists from 14 countries and 13 U.S. states collaborated virtually in the Third Annual Baylor College of Medicine & DNANexus Structural Variation hackathon. The goal of the hackathon was to advance research on structural variants (SVs) by prototyping and iterating on open-source software. This led to nine hackathon projects focused on diverse genomics research interests, including various SV discovery and genotyping methods, SV sequence reconstruction, and clinically relevant structural variation, including SARS-CoV-2 variants. Repositories for the projects that participated in the hackathon are available at

**Open Peer Review**

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REVIEW
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# Asthma and the Missing Heritability Problem: Necessity for Multiomics Approaches in Determining Accurate Risk Profiles

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Asthma is ranked among the most common chronic conditions and has become a significant public health issue due to the recent and rapid increase in its prevalence. Investigations into the underlying genetic factors predict a heritable component for its incidence, estimated between 35% and 90% of causation. Despite the application of large-scale genome-wide association studies (GWAS) and admixture mapping approaches, the proportion of variants identified accounts for less than 15% of the observed heritability of the disease. The discrepancy between the predicted heritable component of disease and the proportion of heritability mapped to the currently identified susceptibility loci has been termed the 'missing heritability problem.' Here, we examine recent studies involving both the analysis of genetically encoded features that contribute to asthma and also the role of non-encoded heritable characteristics, including epigenetic, environmental, and developmental aspects of disease. The importance of vertical maternal microbiome transfer and the influence of maternal immune factors on fetal conditioning in the inheritance of disease are also discussed. In order to highlight the broad array of biological inputs that contribute to the sum of heritable risk factors associated with allergic disease incidence that, together, contribute to the induction of a pro-atopic state. Currently, there is a need to develop in-depth models of asthma risk factors to overcome the limitations encountered in the interpretation of GWAS results in isolation, which have resulted in the missing heritability problem. Hence, multiomics analyses need to be established considering genetic, epigenetic, and functional data to create a true systems biology-based approach for analyzing the regulatory pathways that underlie the inheritance of asthma and to develop accurate risk profiles for disease.

**Keywords: asthma, GWAS - genome-wide association study, inheritability, epigenetics, microbiome and dysbiosis, maternal inheritance, atopic disease, multiomics approach**

Clinical Reviews in Allergy & Immunology
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# Microbial Dysbiosis Tunes the Immune Response Towards Allergic Disease Outcomes

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**Abstract**
The hygiene hypothesis has been popularized as an explanation for the rapid increase in allergic disease observed over the past 50 years. Subsequent epidemiological studies have described the protective effects that in utero and early life exposures to an environment high in microbial diversity have in conferring protective benefits against the development of allergic diseases. The rapid advancement in next generation sequencing technology has allowed for analysis of the diverse nature of microbial communities present in the barrier organs and a determination of their role in the induction of allergic disease. Here, we discuss the recent literature describing how colonization of barrier organs during early life by the microbiota influences the development of the adaptive immune system. In parallel, mechanistic studies have delivered insight into the pathogenesis of disease, by demonstrating the comparative effects of protective T regulatory (Treg) cells, with inflammatory T helper 2 (Th2) cells in the development of immune tolerance or induction of an allergic response. More recently, a significant advancement in our understanding into how interactions between the adaptive immune system and microbially derived factors play a central role in the development of allergic disease has emerged. Providing a deeper understanding of the symbiotic relationship between our microbiome and immune system, which explains key observations made by the hygiene hypothesis. By studying how perturbations that drive dysbiosis of the microbiome can cause allergic disease, we stand to benefit by delineating the protective versus pathogenic aspects of human interactions with our microbial companions, allowing us to better harness the use of microbial agents in the design of novel prophylactic and therapeutic strategies.

**Keywords** Adaptive immunity · Microbiome · CD4 + · Hygiene · Allergy · Atopy

## Introduction

Atopic diseases such as asthma, hay fever, atopic dermatitis, and food allergies represent the most common forms of allergy and are typically defined by the presence of specific immunoglobulin E (sIgE) in serum or a positive skin prick test for common environmental allergens. Constituting the most prevalent chronic condition of childhood, significant proportions of children develop atopic symptoms in their first year of life. One recent multinational study indicated that 14–28% of infants suffer from atopic dermatitis [1] and rates of recurrent, severe wheezing often used as an early diagnostic marker of heightened risk for the development of asthma have been reported at 16% [2], with some western countries reporting rates of food allergy in excess of 10% at 12 months of age [3]. Increases in the prevalence of these conditions have largely been observed in industrialized countries and have been linked to the modern western diet and lifestyle. Although, there is now also growing evidence of increasing rates of disease in rapidly developing countries, showing a correlation with rising economic growth and changes in diet and lifestyle [4]. Numerous studies indicate that these types of allergic responses often occur in a progressive manner termed the "atopic march," initially presenting early in infants as a skin allergy or eczema that is linked to an underlying food allergy [5]. Subsequently, many children go on to become sensitized to indoor allergens, such as dust or pet dander and to develop allergic rhinitis and then asthma later in childhood or in their early teenage years [5]. Sensitization to outdoor aeroallergens such as grass and tree pollens typically occurs during the later phases of the atopic march, at a time where sensitization to

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Review

# Targeting cancer signaling pathways by natural products: Exploring promising anti-cancer agents

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ABSTRACT

Cancer is one of the leading causes of death and significantly burdens the healthcare system. Due to its prevalence, there is undoubtedly an unmet need to discover novel anticancer drugs. The use of natural products as anticancer agents is an acceptable therapeutic approach due to accessibility, applicability, and reduced cytotoxicity. Natural products have been an incomparable source of anticancer drugs in the modern era of drug discovery. Along with their derivatives and analogs, natural products play a major role in cancer treatment by modulating the cancer microenvironment and different signaling pathways. These compounds are effective against several signaling pathways, mainly cell death pathways (apoptosis and autophagy) and embryonic developmental pathways (Notch pathway, Wnt pathway, and Hedgehog pathway). The historical record of natural products is strong, but there is a need to investigate the current role of natural products in the discovery and development of cancer drugs and determine the possibility of natural products being an important source of future therapeutic agents. Many target-specific anticancer drugs failed to provide successful results, which accounts for a need to investigate natural products with multi-target characteristics to achieve better outcomes. The potential of natural products to be promising novel compounds for cancer treatment makes them an important area of research. This review explores the significance of natural products in inhibiting the various signaling pathways that serve as drivers of carcinogenesis and thus pave the way for developing and discovering anticancer drugs.

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ORIGINAL PAPER

# A high-throughput DNA sequencing study of fecal bacteria of seven Mexican horse breeds

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## Abstract

Horses are non-ruminant, herbivorous mammals, been used through history for various purposes, with a gut microbiota from cecum to the colon, possessing remarkable fermentative capacity. We studied the fecal microbiota of Azteca, Criollo, Frisian, Iberian, Pinto, Quarter and Spanish horse breeds living in Mexico by next-generation DNA sequencing of 16S rRNA gene libraries. Dominant phyla Firmicutes, Bacteroidetes, Proteobacteria, Spirochaetes, Fibrobacteres, Actinobacteria and Verrucomicrobia have different relative abundances among breeds, with contrasted alpha and beta diversities as well. Heatmap analysis revealed that Ruminococcaceae, Lachnospiraceae, Mogibacteriaceae families, and order Clostridiales are more abundant in Spanish, Azteca, Quarter and Criollo breeds. The LEfSe analysis displayed higher abundance of order Bacteroidales, family BS11, and genera *Faecalibacterium, Comamonas, Collinsella, Acetobacter*, and *Treponema* in Criollo, Azteca, Iberian, Spanish, Frisian, Pinto, and Quarter horse breeds. The conclusion is that dominant bacterial taxa, found in fecal samples of horse breeds living in Mexico, have different relative abundances.

**Keywords** Horse breeds · Fecal microbiota · High-throughput DNA sequencing · Bacterial diversity · Ion Torrent

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Fernando Hernández Quiroz and Selvasankar Murugesan contributed equally to this work.

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ARTICLE OPEN

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# Patterns and distribution of de novo mutations in multiplex Middle Eastern families

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While de novo mutations (DNMs) are key to genetic diversity, they are also responsible for a high number of rare disorders. To date, no study has systematically examined the rate and distribution of DNMs in multiplex families in highly consanguineous populations. Leveraging WGS profiles of 645 individuals in 146 families, we implemented a combinatorial approach using 3 complementary tools for DNM discovery in 353 unique trio combinations. We found a total of 27,168 DNMs (median: 70 single-nucleotide and 6 insertion-deletions per individual). Phasing revealed around 80% of DNMs were paternal in origin. Notably, using whole-genome methylation data of spermatogonial stem cells, these DNMs were significantly more likely to occur at highly methylated CpGs (OR: 2.03; $p$ value $= 6.62 \times 10^{-11}$). We then examined the effects of consanguinity and ethnicity on DNMs, and found that consanguinity does not seem to correlate with DNM rate, and special attention has to be considered while measuring such a correlation. Additionally, we found that Middle-Eastern families with Arab ancestry had fewer DNMs than African families, although not significant ($p$ value $=$ 0.16). Finally, for families with diseased probands, we examined the difference in DNM counts and putative impact across affected and unaffected siblings, but did not find significant differences between disease groups, likely owing to the enrichment for recessive disorders in this part of the world, or the small sample size per clinical condition. This study serves as a reference for DNM discovery in multiplex families from the globally under-represented populations of the Middle-East.

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## INTRODUCTION

De novo mutations (DNMs) play major roles in organismal evolution, in which they are responsible for creating biological diversity [1]. Though rare, DNMs can also disrupt core developmental pathways, resulting in severe genetic disorders, such as autism spectrum disorder, congenital heart disease, and intellectual disability [2, 3], and could explain the recurrence of such severe disorders in outbred populations despite the detrimental impact on reproductive fitness.

As the interest in understanding the roles of DNMs grows, it has become useful to assess their pattern and distribution in both simplex and multiplex families from ancestries representing the diversity of global populations. The average DNM rate in humans is estimated to be around $1–1.3 \times 10^{-8}$ mutations per base per generation [4–6]. However, estimates are somewhat complicated by the coverage efficiency in both parents and their children and by the genomic context, e.g., the higher mutation rates in GC-rich regions across different organisms, including humans [7, 8]. Moreover, considering the technical challenges produced by PCR bias or sequencing errors, and the relatively low number of DNMs in the genome, accurate calling and detection requires approaches that can yield the highest sensitivity without compromising specificity; and such combinatorial approaches must be developed using complementary tools that help increase the likelihood of capturing true positives while limiting erroneous calls.

While previous studies have looked at DNMs in different populations [4–6, 8–12], they have been somewhat limited by the use of separate parent-offspring trios or a small number of multi-generational families. Further, most studies to date have been performed in outbred populations, with inadequate representation of the highly consanguineous Middle Eastern cohorts. We thus aimed to explore the rate and distribution of single-gamete DNMs detected using short-read whole-genome sequencing (WGS) in a cohort of 146 multi-offspring families (353 unique trios) enrolled in a large pediatric tertiary care center in the Middle East. We applied three complementary tools to generate an integrated list of DNMs for every individual, which was used to estimate the DNM rate, determine the parent-of-origin, and investigate the impact of parental age on DNM count. We also examined the DNM mutational spectra and the distribution of DNMs through genome methylation maps for both gonadal and somatic tissues. Finally, we investigated the impact of consanguinity, ancestry, and disease status on DNM counts in our cohort. To the best of our knowledge, this is the first large-scale assessment of DNMs in a Middle Eastern multiplex family cohort, and it establishes a reference for this globally under-represented population.

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# Surface Modification of Polytetrafluoroethylene and Polycaprolactone Promoting Cell-Selective Adhesion and Growth of Valvular Interstitial Cells

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**Abstract:** Tissue engineering concepts, which are concerned with the attachment and growth of specific cell types, frequently employ immobilized ligands that interact preferentially with cell types of interest. Creating multicellular grafts such as heart valves calls for scaffolds with spatial control over the different cells involved. Cardiac heart valves are mainly constituted out of two cell types, endothelial cells and valvular interstitial cells. To have control over where which cell type can be attracted would enable targeted cell settlement and growth contributing to the first step of an engineered construct. For endothelial cells, constituting the outer lining of the valve tissue, several specific peptide ligands have been described. Valvular interstitial cells, representing the bulk of the leaflet, have not been investigated in this regard. Two receptors, the integrin α9β1 and CD44, are known to be highly expressed on valvular interstitial cells. Here, we demonstrate that by covalently grafting the corresponding peptide and polysaccharide ligand onto an erodible, polycaprolactone (PCL), and a non-degradable, polytetrafluoroethylene (PTFE), polymer, surfaces were generated that strongly support valvular interstitial cell colonization with minimal endothelial cell and reduced platelet adhesion. The technology for covalent binding of corresponding ligands is a key element towards tissue engineered cardiac valves for in vitro applications, but also towards future in vivo application, especially in combination with degradable scaffold material.

**Keywords:** valvular interstitial cells; surface modification; vascular tissue engineering; hyaluronic acid; integrin; CD44; PTFE; PCL; bioconjugation



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## 1. Introduction

A wide range of materials are used for medical devices and other medical applications from a simple mechanical support up to the replacement of organ functions. The application of surface modification of biomaterials opens new possible applications that have been widely discussed [1]. It is important that the surface of the foreign material does not cause unwanted host responses that would impair the intended function. A desirable material would show both inert characteristics, such as antifouling [2–4], and promotion of colonization with specific cell types [5]. The methods most frequently used include plasma techniques [6] as well as chemical treatments, e.g., wet chemistry [7], to name but a few. Apart from simple coating with proteins of the extracellular matrix (ECM), more advanced techniques make use of covalent conjugation of ECM-derived recognition motifs such as the well-known "RGD" motif [5]. Additional peptides have been described addressing specific cell types, e.g., the amino acid sequences REDV and YIGSR were found to interact with endothelial cells in a selective manner [8–10]. Besides in vivo applications, the increasing

Original research

# Activation of NOTCH signaling via DLL1 is mediated by APE1-redox-dependent NF-κB activation in oesophageal adenocarcinoma

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## ABSTRACT

**Objective** Oesophageal adenocarcinoma (EAC) arises in the setting of Barrett's oesophagus, an intestinal metaplastic precursor lesion that can develop in patients with chronic GERD. Here, we investigated the role of acidic bile salts, the mimicry of reflux, in activation of NOTCH signaling in EAC.

**Design** This study used public databases, EAC cell line models, L2-IL1β transgenic mouse model and human EAC tissue samples to identify mechanisms of NOTCH activation under reflux conditions.

**Results** Analysis of public databases demonstrated significant upregulation of NOTCH signaling components in EAC. In vitro studies demonstrated nuclear accumulation of active NOTCH1 cleaved fragment (NOTCH intracellular domain) and upregulation of NOTCH targets in EAC cells in response to reflux conditions. Additional investigations identified DLL1 as the predominant ligand contributing to NOTCH1 activation under reflux conditions. We discovered a novel crosstalk between APE1 redox function, reflux-induced inflammation and DLL1 upregulation where NF-κB can directly bind to and induce the expression of DLL1. The APE1 redox function was crucial for activation of the APE1-NF-κB-NOTCH axis and promoting cancer cell stem-like properties in response to reflux conditions. Overexpression of APE1 and DLL1 was detected in gastro-oesophageal junctions of the L2-IL1ß transgenic mouse model and human EAC tissue microarrays. DLL1 high levels were associated with poor overall survival in patients with EAC.

**Conclusion** These findings underscore a unique mechanism that links redox balance, inflammation and embryonic development (NOTCH) into a common pro-tumorigenic pathway that is intrinsic to EAC cells.

### WHAT IS ALREADY KNOWN ON THIS SUBJECT?

⇒ Apurinic/apyrimidinic endonuclease (APE1) is aberrantly overexpressed in multiple cancer types, including oesophageal adenocarcinoma (EAC). Exposure to chronic gastro-oesophageal reflux, the main risk factor for Barrett's oesophagus (BE)-originated oesophageal tumourigenesis, induces APE1 dysregulation, activates intricate networks of redox-dependent transcription factors and promotes cancer cell survival.

⇒ Although activation of NOTCH signaling was reported in BE and EAC, the mechanisms underlying its activation in reflux conditions remain largely unknown.

### WHAT ARE THE NEW FINDINGS?

⇒ Using 2D and 3D in vitro models as well as mouse and human data, we report a novel signaling axis where APE1 promotes activation of NOTCH through redox-dependent NF-κB activation and DLL1 induction. High levels of DLL1 are associated with poor overall survival in patients with EAC.

### HOW MIGHT IT IMPACT ON CLINICAL PRACTICE IN THE FORESEEABLE FUTURE?

⇒ EAC is one of the leading causes of cancer death in the USA and Western countries, where standard chemotherapy has limited efficacy. Our findings provide a new perspective for the crosstalk between signaling networks, suggesting that targeting NOTCH or APE1-redox function can be a promising therapeutic strategy in patients with EAC.

## INTRODUCTION

Oesophageal cancer is the sixth leading cause of cancer death worldwide.[1] Oesophageal adenocarcinoma (EAC), the predominant histopathological type of oesophageal cancer in the USA and Western countries, has been increasing rapidly over the past 40 years.[2] Patients with EAC have a 5-year survival rate below 20%.[3 4] Hence, there is an urgent need to identify novel molecular mechanisms and find new therapeutic targets for EAC. Chronic GERD is characterised by abnormal exposure of the lower oesophagus to a mixture of acidic gastric juice and bile salts. GERD is the main risk factor for metaplastic Barrett's oesophagus (BE) and its progression to EAC.[5 6] GERD conditions in patients with BE and EAC induce DNA damage along with aberrant activation of pro-inflammatory and pro-tumorigenic signaling pathways such as NF-κB and STAT3 pathways.[7 8]



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REVIEW
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# Infections and Pregnancy: Effects on Maternal and Child Health

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Pregnancy causes physiological and immunological adaptations that allow the mother and fetus to communicate with precision in order to promote a healthy pregnancy. At the same time, these adaptations may make pregnant women more susceptible to infections, resulting in a variety of pregnancy complications; those pathogens may also be vertically transmitted to the fetus, resulting in adverse pregnancy outcomes. Even though the placenta has developed a robust microbial defense to restrict vertical microbial transmission, certain microbial pathogens have evolved mechanisms to avoid the placental barrier and cause congenital diseases. Recent mechanistic studies have begun to uncover the striking role of the maternal microbiota in pregnancy outcomes. In this review, we discuss how microbial pathogens overcome the placental barrier to cause congenital diseases. A better understanding of the placental control of fetal infection should provide new insights into future translational research.

**Keywords: preterm labor, miscarriage, TORCH, pregnancy complications, microbiome**

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## 1 INTRODUCTION

Pregnancy is a critical "formative period" that has a significant impact on an individual's health trajectory from fetal life to adulthood (Lash, 2015). Pregnancy is governed by a series of interconnected physiological and cellular mechanisms that promote maternal homeostasis and maintain optimal maternal-fetal interface while boosting fetal growth (Ander et al., 2019). These mechanisms enable the woman's body to undergo, physiological and immunologic adaptations to host fetal antigens. From the mother's immune system perspective, the fetus is an allograft that contains foreign antigens from the father (Robinson and Klein, 2012). To protect the fetus from immune rejection, the maternal immune must strike a delicate balance between maintaining tolerance to the fetal allograft by inducing anti-inflammatory properties at the maternal-fetal interface and maintaining an elevated inflammatory response with rising levels of pro-inflammatory cytokines at mucosal surfaces such as the gut to protect against microbial challenges (Koren et al., 2012; Erlebacher, 2013; PrabhuDas et al., 2015; Nuriel-Ohayon et al., 2016; Marchant et al., 2017). Concurrently, the transition of the maternal immune system during pregnancy from more inflammatory states at the start of pregnancy to lower levels of inflammation in mid-pregnancy makes pregnant women more vulnerable to infections (Mor and Cardenas, 2010) and pregnancy complications. Although the exact etiology of pregnancy complications remains elusive, the complex interaction of microbial or other factors with host immune system is thought to be the underlying pathogenesis of pregnancy complications (Megli and Coyne, 2021).

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ORIGINAL RESEARCH
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# Epigenetic DNA Methylation Signatures Associated With the Severity of Paget's Disease of Bone

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**Background:** Paget's disease of bone (PDB) is characterized by focal areas of dysregulated bone turnover resulting in increased bone loss and abnormal bone formation with variable severity. PDB has a complex etiology and both genetics and environmental factors have been implicated. A recent study has identified many differentially methylated loci in PDB compared to healthy subjects. However, associations between DNA methylation profiles and disease severity of PDB have not been investigated.

**Objectives:** To investigate the association between DNA methylation signals and PDB severity.

**Methods:** Using 232 well-characterized PDB subjects from the PRISM trial, a disease severity score was devised based on the clinical features of PDB. DNA methylation profiling was performed using Illumina Infinium HumanMethylation 450K array.

**Results:** We identified 100 CpG methylation sites significantly associated with PDB severity at FDR <0.05. Additionally, methylation profiles in 11 regions showed Bonferroni-significant association with disease severity including six islands (located in *VCL*, *TBX5*, *CASZ1*, *ULBP2*, *NUDT15* and *SQSTM1*), two gene bodies (*CXCR6* and *DENND1A*), and 3 promoter regions (*RPL27*, *LINC00301* and *VPS29*). Moreover, FDR-significant effects from region analysis implicated genes with genetic variants previously associated with PDB severity, including *RIN3* and *CSF1*. A multivariate predictor model featuring the top severity-associated CpG sites revealed a significant correlation ($R = 0.71$, $p = 6.9 \times 10^{-16}$) between observed and predicted PDB severity scores. On dichotomizing the severity scores into low and high severity, the model featured an area under curve (AUC) of 0.80, a sensitivity of 0.74 and a specificity of 0.68.

**Conclusion:** We identified several CpG methylation markers that are associated with PDB severity in this pioneering study while also highlighting the novel molecular pathways associated with disease progression. Further work is warranted to affirm the suitability of our model to predict the severity of PDB in newly diagnosed patients or patients with family history of PDB.

**Keywords: paget's disease of bone, bone, epigenetics, DNA methylation, genetics**

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molecules

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*Article*

# Molecular Analysis and Conformational Dynamics of Human MC4R Disease-Causing Mutations

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**Abstract:** Obesity is a chronic disease with increasing cases among children and adolescents. Melanocortin 4 receptor (MC4R) is a G protein-coupled transporter involved in solute transport, enabling it to maintain cellular homeostasis. MC4R mutations are associated with early-onset severe obesity, and the identification of potential pathological variants is crucial for the clinical management of patients with obesity. A number of mutations have been reported in MC4R that are responsible for causing obesity and related complications. Delineating these mutations and analyzing their effect on MC4R's structure will help in the clinical intervention of the disease condition as well as designing potential drugs against it. Sequence-based pathogenicity and structure-based protein stability analyses were conducted on naturally occurring variants. We used computational tools to analyze the conservation of these mutations on MC4R's structure to map the structural variations. Detailed structural analyses were carried out for the active site mutations (i.e., D122N, D126Y, and S188L) and their influence on the binding of calcium and the agonist or antagonist. We performed molecular dynamics (MD) simulations of the wild-type and selected mutations to delineate the conformational changes, which provided us with possible reasons for MC4R's instability in these mutations. This study provides insight into the potential direction toward understanding the molecular basis of MC4R dysfunction in disease progression and obesity.

**Keywords:** MC4R; G protein-coupled transporter (GPCR); obesity; pathological variants; mutational analysis; simulation



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## 1. Introduction

Obesity forms a complex multifactorial disease, with a global prevalence of 12%. Studies have suggested a strong genetic influence affecting obesity, with the melanocortin 4 receptor (MC4R) being one of the most critical and widely investigated so far. It is a member of the G protein-coupled receptor (GPCR) family, a major drug target accounting for 30% of FDA-approved medicine [1,2]. MC4R is expressed in the hypothalamus (i.e., paraventricular nucleus), and it is a key component of the leptin–melanocortin pathway [3]. The MC4R is activated by proopiomelanocortin (POMC)-derived polypeptides: α- and β-melanocyte-stimulating hormone (MSH), released by the post-translational processing of POMC. Conversely it is blocked by agouti-related peptide (AgRP) expressed in the AgRP/neuropeptide Y(NPY) neurons in the arcuate nucleus [4]. The function of these neurons is regulated via signals received from adipose tissue, precisely by leptin via the leptin receptor in the case of food and energy metabolism. MSH activates the MC4R and catalyzes the exchange of GDP for GTP on the stimulatory G protein (Gs), resulting in activation of adenylyl cyclase (AC) and generation of intracellular cAMP. cAMP activates protein kinase A(PKA) or MAPK signaling (via ERK1/2 phosphorylation) [5,6]. However, more

JEM Journal of Experimental Medicine

BRIEF DEFINITIVE REPORT

# Respiratory viral infections in otherwise healthy humans with inherited IRF7 deficiency

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**Autosomal recessive IRF7 deficiency was previously reported in three patients with single critical influenza or COVID-19 pneumonia episodes. The patients' fibroblasts and plasmacytoid dendritic cells produced no detectable type I and III IFNs, except IFN-β. Having discovered four new patients, we describe the genetic, immunological, and clinical features of seven IRF7-deficient patients from six families and five ancestries. Five were homozygous and two were compound heterozygous for IRF7 variants. Patients typically had one episode of pulmonary viral disease. Age at onset was surprisingly broad, from 6 mo to 50 yr (mean age 29 yr). The respiratory viruses implicated included SARS-CoV-2, influenza virus, respiratory syncytial virus, and adenovirus. Serological analyses indicated previous infections with many common viruses. Cellular analyses revealed strong antiviral immunity and expanded populations of influenza- and SARS-CoV-2–specific memory CD4$^+$ and CD8$^+$ T cells. IRF7-deficient individuals are prone to viral infections of the respiratory tract but are otherwise healthy, potentially due to residual IFN-β and compensatory adaptive immunity.**

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## Introduction

Human type I IFN–mediated immunity provides an intrinsic, innate first line of defense against invading viruses (Lazear et al., 2019; Schneider et al., 2014). The 17 type I IFN genes encode 13 forms of IFN-α, IFN-β, IFN-ε, IFN-κ, and IFN-ω. All nucleated cells can produce IFN-β upon sensing viral infection, and this contributes to the induction of other type I IFNs. During viral infections, plasmacytoid dendritic cells (pDCs) produce large quantities of IFN-α and -ω (Cella et al., 1999; Reizis, 2019; Siegal et al., 1999). IFN-κ and IFN-ε are preferentially expressed in the skin and reproductive tract, respectively, and are three orders of magnitude less potent than IFN-α2 (Fung et al., 2013; Harris et al., 2018; LaFleur et al., 2001). Nucleated cells express type I IFN receptors, whereupon stimulation induces the transcription of type I IFN genes and other IFN-stimulated genes (ISGs), most of which promote antiviral immunity (Schoggins, 2019). Notably, however, human pluripotent stem cells constitutively express ISGs and display attenuated induction of ISGs upon type I IFN stimulation (Hong and Carmichael, 2013; Wu et al., 2018).

*Ifnar1* or *Ifnar2* knockout mice that lack the type I IFN receptor are susceptible to many experimental infections, but an unexpected pattern is emerging in humans, with the corresponding deficits seeming to confer vulnerability to a narrower range of viruses (Duncan et al., 2021; Meyts and Casanova, 2021). Autosomal recessive (AR) IFNAR1 and IFNAR2 deficiencies have been reported in 16 and 9 patients, respectively (Abolhassani et al., 2022; Bastard et al., 2022; Bastard et al., 2021; Duncan et al., 2015; Duncan et al., 2022; Gothe et al., 2020; Hernandez et al., 2019; Zhang et al., 2020). Patients with inherited STAT2 or IRF9 deficiency lack ISG factor 3 (ISGF-3)—a transcription factor complex consisting of STAT1, STAT2, and IRF9 that normally induces ISG expression in response to type I and type III IFNs—but these patients have a similarly narrower range of viral susceptibility (Alosaimi et al., 2019; Hambleton et al., 2013; Hernandez et al., 2018; Moens et al., 2017).

Patients with an apparent complete absence of type I IFN immunity (IFNAR1, IFNAR2) or of ISGF-3 (STAT2, IRF9) are prone to adverse reactions to live attenuated viral vaccines, such as yellow fever virus 17D (YFV-17D) and the measles, mumps, and rubella virus (MMR) vaccine, and are also susceptible to HSV-1, encephalitis, and critical influenza or COVID-19 pneumonia (Abolhassani et al., 2022; Alosaimi et al., 2019; Bastard et al., 2021; Bastard et al., 2022; Duncan et al., 2015; Duncan et al., 2022; Hambleton et al., 2013; Hernandez et al., 2019; Hernandez et al., 2018; Moens et al., 2017; Zhang et al., 2020). The clinical penetrance of such infections in patients with type I IFN deficiencies remains unclear. These patients seem to be otherwise normally resistant to a number of common viruses. By contrast, AR complete and partial STAT1-deficient patients, with impairments of both ISGF-3 and γ-activated factor and, thus, unresponsive to type I, II, and III IFNs, are prone to various viral and intramacrophagic infections, resulting in early-onset disease following a devastating course (Boehmer et al., 2020; Burns et al., 2016; Chapgier et al., 2006; Dupuis et al., 2003; Le Voyer et al., 2021; Sakata et al., 2020; Vairo et al., 2011).

IRFs are a family of transcription factors initially identified on the basis of their ability to promote type I IFN production (Miyamoto et al., 1988). IRF3 and IRF7 have been implicated in the transcription of type I IFN genes downstream from viral sensors, whereas other members of the IRF family promote the transcription of a subset of ISGs (e.g., IRF9) or regulate leukocyte development and differentiation (e.g., IRF8). These IRFs typically bind regulatory DNA elements similar to those bound by ISGF-3 (IFN-stimulated response element boxes). Studies of knockout mice have revealed a key role for IRF7 in the production of type I and III IFNs (Honda et al., 2005). These studies also showed that pDCs are the most potent type I and III IFN-producing cells, because of their markedly high levels of constitutive IRF7 expression (Colonna et al., 2004; Honda and Taniguchi, 2006; Liu, 2001; Reizis, 2019). *Irf7*-knockout mice are much more susceptible to fatal HSV-1, encephalomyocarditis virus, and influenza A virus (IAV) infections than either WT or *Irf3*-knockout mice, indicating a requirement for IRF7 in immunity to both DNA and RNA viruses (Hatesuer et al., 2017; Honda et al., 2005).

In humans, a 2.5-yr-old child with life-threatening influenza virus pneumonia was found to be compound heterozygous for loss-of-function (LoF) *IRF7* variants (Ciancanelli et al., 2015). This case confirmed the requirement for IRF7 for the induction of all type I and III IFNs, with the exception of IFN-β. More recently, two unrelated and previously healthy adults presented with life-threatening COVID-19 pneumonia due to inherited IRF7 deficiency (Zhang et al., 2020). Surprisingly, neither of these patients presented any clinically severe viral infections until the ages of 49 and 50 yr. This raises important questions regarding the requirement for IRF7-dependent type I and III IFNs for human immunity to viruses. With brief descriptions of only three patients, the range of severe viral infections and the individual penetrance of each viral infection in patients with inherited IRF7 deficiency remained unclear. Here, we studied the genetic, immunological, and clinical features of an international cohort of seven patients from six kindreds and five ancestries with AR IRF7 deficiency, including the three previously described patients.

## Results and discussion

### Patients with biallelic rare *IRF7* variants

In 2015, we reported AR IRF7 deficiency in a single patient with life-threatening influenza pneumonia (P1, F410V;Q421X; Ciancanelli et al., 2015). In 2020, we reported another two patients with AR IRF7 deficiency (P2, P364AfsX38;P364AfsX38 and P3, D117N;M371V) and life-threatening COVID-19 pneumonia, providing proof-of-principle that critical influenza and COVID-19 pneumonia can be allelic (Casanova and Abel, 2021; Zhang et al., 2022; Zhang et al., 2020). We have now performed whole-exome sequencing (WES) or whole-genome sequencing on the COVID Human Genetic Effort cohort of 927 adult patients with critical COVID-19 pneumonia (Casanova et al., 2020). We have also analyzed a cohort of 107 patients with severe influenza pneumonia. We searched for patients with biallelic very rare variants of *IRF7* (minor allele frequency [MAF] <0.001).

In addition to the three previously reported patients with critical influenza or COVID-19 pneumonia, we identified one

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# Presymptomatic diagnosis of postoperative infection and sepsis using gene expression signatures

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## Abstract

**Purpose:** Early accurate diagnosis of infection ± organ dysfunction (sepsis) remains a major challenge in clinical practice. Utilizing effective biomarkers to identify infection and impending organ dysfunction before the onset of clinical signs and symptoms would enable earlier investigation and intervention. To our knowledge, no prior study has specifically examined the possibility of pre-symptomatic detection of sepsis.

**Methods:** Blood samples and clinical/laboratory data were collected daily from 4385 patients undergoing elective surgery. An adjudication panel identified 154 patients with definite postoperative infection, of whom 98 developed sepsis. Transcriptomic profiling and subsequent RT-qPCR were undertaken on sequential blood samples taken postoperatively from these patients in the three days prior to the onset of symptoms. Comparison was made against postoperative day-, age-, sex- and procedure- matched patients who had an uncomplicated recovery ($n$ =151) or postoperative inflammation without infection ($n$ =148).

**Results:** Specific gene signatures optimized to predict infection or sepsis in the three days prior to clinical presentation were identified in initial discovery cohorts. Subsequent classification using machine learning with cross-validation with separate patient cohorts and their matched controls gave high Area Under the Receiver Operator Curve (AUC) values. These allowed discrimination of infection from uncomplicated recovery (AUC 0.871), infectious from non-infectious systemic inflammation (0.897), sepsis from other postoperative presentations (0.843), and sepsis from uncomplicated infection (0.703).

**Conclusion:** Host biomarker signatures may be able to identify postoperative infection or sepsis up to three days in advance of clinical recognition. If validated in future studies, these signatures offer potential diagnostic utility for postoperative management of deteriorating or high-risk surgical patients and, potentially, other patient populations.

**Keywords:** Sepsis, Diagnosis, Host, Biomarker, Signatures

## Introduction

Sepsis, the dysregulated host response to infection leading to life-threatening organ dysfunction [1], is a substantial global cause of mortality and morbidity [2]. Early, accurate diagnosis of infection and organ dysfunction remains problematic, as reflected by multiple

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# Bioinformatics Analysis Reveals FOXM1/BUB1B Signaling Pathway as a Key Target of Neosetophomone B in Human Leukemic Cells: A Gene Network-Based Microarray Analysis

*Shilpa Kuttikrishnan[1,2†], Tariq Masoodi[3†], Gulab Sher[1], Ajaz A. Bhat[3], Kalyani Patil[1], Tamam El-Elimat[4], Nicholas H. Oberlies[5], Cedric J. Pearce[6], Mohmmad Haris[3,7], Aamir Ahmad[1,8], Feras Q. Alali[2] and Shahab Uddin[1,7,8*]*

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Abnormal expression of Forkhead box protein M1 (FOXM1) and serine/threonine kinase Budding uninhibited by benzimidazoles 1 (BUB1B) contributes to the development and progression of several cancers, including chronic myelogenous leukemia (CML). However, the molecular mechanism of the FOXM1/BUB1B regulatory network and the role of Neosetophomone-B (NSP-B) in leukemia remains unclear. NSP-B, a meroterpenoid fungal secondary metabolite, possesses anticancer potential in human leukemic cells lines; however, the underlying mechanism has not been elucidated. The present study aimed to explore the role of NSP-B on FOXM1/BUB1B signaling and the underlying molecular mechanism of apoptosis induction in leukemic cells. We performed gene expression profiling of NSP-B-treated and untreated leukemic cells to search for differentially expressed genes (DEGs). Interestingly *BUB1B* was found to be significantly downregulated (logFC -2.60, adjusted p = 0.001) in the treated cell line with the highest connectivity score among cancer genes. Analysis of TCGA data revealed overexpression of *BUB1B* compared to normal in most cancers and overexpression was associated with poor prognosis. *BUB1B* also showed a highly significant positive correlation with *FOXM1* in all the TCGA cancer types. We used human leukemic cell lines (K562 and U937) as an *in vitro* study model to validate our findings. We found that NSP-B treatment of leukemic cells suppressed the expression of FOXM1 and BUB1B in a dose-dependent manner. In addition, NSP-B also resulted in the downregulation of FOXM1-regulated genes such as Aurora kinase A, Aurora kinase B, CDK4, and CDK6. Suppression of FOXM1 either by siRNA or NSP-B reduced BUB1B expression and enhanced cell survival inhibition and induction of apoptosis. Interestingly combination treatment of thiostrepton and NSP-B

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# The Prevalence and Genetic Spectrum of Familial Hypercholesterolemia in Qatar Based on Whole Genome Sequencing of 14,000 Subjects

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Familial hypercholesterolemia (FH) is an inherited disease characterized by reduced efficiency of low-density lipoprotein-cholesterol (LDL-C) removal from the blood and, consequently, an increased risk of life-threatening early cardiovascular complications. In Qatar, the prevalence of FH has not been determined and the disease, as in many countries, is largely underdiagnosed. In this study, we combined whole-genome sequencing data from the Qatar Genome Program with deep phenotype data from Qatar Biobank for 14,056 subjects to determine the genetic spectrum and estimate the prevalence of FH in Qatar. We used the Dutch Lipid Clinic Network (DLCN) as a diagnostic tool and scrutinized 11 FH-related genes for known *pathogenic* and *possibly pathogenic* mutations. Results revealed an estimated prevalence of 0.8% (1:125) for definite/probable cases of FH in the Qatari population. We detected 16 known *pathogenic/likely pathogenic* mutations in *LDLR* and one in *PCSK9;* all in a heterozygous state with high penetrance. The most common mutation was rs1064793799 (c.313+3A >C) followed by rs771019366 (p.Asp90Gly); both in *LDLR*. In addition, we identified 18 highly penetrant *possibly pathogenic* variants, of which 5 were Qatari-specific, in *LDLR*, *APOB*, *PCSK9* and *APOE*, which are predicted to be among the top 1% most deleterious mutations in the human genome but further validations are required to confirm their pathogenicity. We did not detect any homozygous FH or autosomal recessive mutations in our study cohort. This pioneering study provides a reliable estimate of FH prevalence in Qatar based on a significantly large population-based cohort, whilst uncovering the spectrum of genetic variants associated with FH.

**Keywords: dyslipidemias, hypercholesterolemia, familial hypercholesterolemia, monogenic, FH, LDL-C, LDLR**

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# AXL Promotes Metformin-Induced Apoptosis Through Mediation of Autophagy by Activating ROS-AMPK-ULK1 Signaling in Human Esophageal Adenocarcinoma

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AXL receptor tyrosine kinase promotes an invasive phenotype and chemotherapy resistance in esophageal adenocarcinoma (EAC). AXL has been implicated in the regulation of autophagy, but the underlying molecular mechanism remains poorly understood. Herein, we investigate the mechanistic role of AXL in autophagy as well as metformin-induced effects on the growth and survival of EAC. We demonstrate that AXL mediates autophagic flux through activation of AMPK-ULK1 signaling in a reactive oxygen species (ROS)-dependent mechanism by glucose starvation. AXL positively regulates basal cellular ROS levels without significantly affecting mitochondrial ROS production in EAC cells. Pharmacological inhibition of cellular ROS using Trolox abrogates glucose starvation-induced AMPK signaling and autophagy. We demonstrate that AXL expression is required for metformin-induced apoptosis in EAC cells *in vitro*. The apoptosis induction by metformin is markedly attenuated by inhibition of autophagy through genetic silencing of Beclin1 or ATG7 autophagy mediators, thereby confirming the requirement of intact autophagy for enhancing metformin-induced apoptosis in EAC cells. Our data indicate that metformin-induced autophagy displays a pro-apoptotic function in EAC cells. We show that the metformin-induced suppression of tumor growth *in vivo* is highly dependent on AXL expression in a tumor xenograft mouse model of EAC. We demonstrate that AXL promotes metformin-induced apoptosis through activation of autophagy in EAC. AXL may be a valuable biomarker to identify tumors that are sensitive to metformin. Therefore, AXL expression could inform the selection of patients for future clinical trials to evaluate the therapeutic efficacy of metformin in EAC.

**Keywords: AMPK, autophagic flux, ATG7, Barrett's esophagus, Beclin1, glucose starvation, proliferation, reactive oxygen species**

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# Identification of Prognostic Metabolomic Biomarkers at the Interface of Mortality and Morbidity in Pre-Existing TB Cases Infected With SARS-CoV-2

*Ilhame Diboun[1†‡], Farhan S. Cyprian[2‡], Najeha Rizwana Anwardeen[3‡], Hadi M. Yassine[3‡], Mohamed A. Elrayess[3], Samreen Mumtaz Rahmoon[2], Sarah Khaled Sayed[2], Sven Schuchardt[4], Malkan Khatib[2], Devendra Bansal[5], Elmoubashar Abu Baker Abd Farag[5], Mohamed M. Emara[2*] and Abdallah M. Abdallah[2*]*

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection currently remains one of the biggest global challenges that can lead to acute respiratory distress syndrome (CARDS) in severe cases. In line with this, prior pulmonary tuberculosis (TB) is a risk factor for long-term respiratory impairment. Post-TB lung dysfunction often goes unrecognized, despite its relatively high prevalence and its association with reduced quality of life. In this study, we used a metabolomics analysis to identify potential biomarkers that aid in the prognosis of COVID-19 morbidity and mortality in post-TB infected patients. This analysis involved blood samples from 155 SARS-CoV-2 infected adults, of which 23 had a previous diagnosis of TB (post-TB), while 132 did not have a prior or current TB infection. Our analysis indicated that the vast majority (~92%) of post-TB individuals showed severe SARS-CoV-2 infection, required intensive oxygen support with a significantly high mortality rate (52.2%). Amongst individuals with severe COVID-19 symptoms, we report a significant decline in the levels of amino acids, notably the branched chains amino acids (BCAAs), more so in the post-TB cohort (FDR <= 0.05) in comparison to mild and asymptomatic cases. Indeed, we identified betaine and BCAAs as potential prognostic metabolic biomarkers of severity and mortality, respectively, in COVID-19 patients who have been exposed to TB. Moreover, we identified serum alanine as an important metabolite at the interface of severity and mortality. Hence, our data associated COVID-19 mortality and morbidity with a long-term metabolically driven consequence of TB infection. In summary, our study provides evidence for a higher mortality rate among COVID-19 infection patients who have history of prior TB infection diagnosis, which mandates validation in larger population cohorts.

**Keywords: COVID-19 disease severity, tuberculosis, post-tuberculosis long-term consequences, metabolomics, biomarkers**

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CANCER COMMUNICATIONS Open Access

REVIEW

# Cytokine- and chemokine-induced inflammatory colorectal tumor microenvironment: Emerging avenue for targeted therapy

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**Abbreviations:** APC, adenomatous polyposis coli; CAFs, cancer-associated fibroblasts; CCL3, C-C motif chemokine ligand 3; CCR6, chemokine receptor 6; CDH1, cadherin 1; COX-2, cyclooxygenase-2; CRC, colorectal cancer; CSF1, colony-stimulating factor 1; CSF2, colony stimulating factor 2; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CTLs, cytotoxic T lymphocytes; CXCL, C-X-C motif chemokine ligand; CXCR, C-X-C chemokine receptor; DCs, dendritic cells; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; eNOS, endothelial nitric oxide synthase; FC$\gamma$R3, immunoglobulin G Fc Receptor 3; FOXP3, forkhead box P3; FRA1, fos-related antigen 1; GM-CSF, granulocyte-macrophage colony-stimulating factor; GP130, glycoprotein 130; GSK3$\beta$, glycogen synthase kinase 3 beta; HMGA1, high mobility group AT-hook 1; HMGB1, high mobility group box 1; IBDs, inflammatory bowel diseases; ICAM-1, intercellular adhesion molecule 1; IDO, indoleamine 2,3-dioxygenase; IL, interleukin; IL-1$\beta$, interleukin-1 beta; Lin$^-$HLA-DR$^-$, lineage negative-human leukocyte antigen-DR isotype; LRG1, leucine rich alpha-2-glycoprotein 1; MAPK, mitogen-activated protein kinase; MCAM, melanoma cell adhesion molecule; M-CSF, macrophage colony-stimulating factor; MDSCs, myeloid-derived suppressor cells; MHC1, major histocompatibility complex class 1; MMP-9, matrix metalloproteinase-9; NF-$\kappa$B, nuclear factor kappa-light-chain-enhancer of activated B cells; NK, natural killer; OCT4, octamer-binding transcription factor 4; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PMN, pre-metastatic niche; RNS, reactive nitrogen species; ROR$\gamma$t, retinoic-acid-receptor-related orphan nuclear receptor gamma; ROS, reactive oxygen species; RUNX1, runt-related transcription factor 1; SIPR1, sphingosine-1-phosphate receptor 1; SMAD4, SMAD family member 4; SNAI2, snail family transcriptional repressor 2; SNAIL, zinc finger protein SNAI1; SOCS3, suppressor of cytokine signaling 3; SOX2, SRY-box transcription factor 2; STAT3, signal transducer and activator of transcription 3; TAMs, tumor-associated macrophages; TCF4, transcription factor 4; TCGA, The Cancer Genome Atlas; TCR, T-cell receptor; TFAP4, transcription factor activating enhancer-binding protein 4; Th1, T-helper 1; TILs, tumor-infiltrating lymphocytes; TME, tumor microenvironment; TNF-$\alpha$, tumor necrosis factor-$\alpha$; TRAF6, TNF receptor associated factor 6; Tregs, T-regulatory cells; TRIM47, tripartite motif containing 47; TSP-1, thrombospondin-1; TWIST1, twist-related protein 1; VEGFA, vascular endothelial growth factor A; ZEB1, zinc finger E-box-binding homeobox 1; $\alpha$-SMA, alpha-smooth muscle actin.

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## Abstract

Colorectal cancer (CRC) is a predominant life-threatening cancer, with liver and peritoneal metastases as the primary causes of death. Intestinal inflammation, a known CRC risk factor, nurtures a local inflammatory environment enriched with tumor cells, endothelial cells, immune cells, cancer-associated fibroblasts, immunosuppressive cells, and secretory growth factors. The complex interactions of aberrantly expressed cytokines, chemokines, growth factors, and matrix-remodeling enzymes promote CRC pathogenesis and evoke systemic responses that affect disease outcomes. Mounting evidence suggests that these cytokines and chemokines play a role in the progression of CRC through immunosuppression and modulation of the tumor microenvironment, which is partly achieved by the recruitment of immunosuppressive cells. These cells impart features such as cancer stem cell-like properties, drug resistance, invasion, and formation of the premetastatic niche in distant organs, promoting metastasis and aggressive CRC growth. A deeper understanding of the cytokine- and chemokine-mediated signaling networks that link tumor progression and metastasis will provide insights into the mechanistic details of disease aggressiveness and facilitate the development of novel therapeutics for CRC. Here, we summarized the current knowledge of cytokine- and chemokine-mediated crosstalk in the inflammatory tumor microenvironment, which drives immunosuppression, resistance to therapeutics, and metastasis during CRC progression. We also outlined the potential of this crosstalk as a novel therapeutic target for CRC. The major cytokine/chemokine pathways involved in cancer immunotherapy are also discussed in this review.

**KEYWORDS**
chemokine, colorectal cancer, cytokine, drug resistance, epithelial-mesenchymal transition, immunosuppression, immunotherapy, inflammation, metastasis, tumor microenvironment

## 1 | BACKGROUND

Colorectal cancer (CRC) is the fourth most common cancer and the third leading cause of cancer-associated death worldwide [1]. Approximately 25% of patients with CRC have metastases at diagnosis, most commonly liver metastases [2]. Peritoneal cavity metastases develop in approximately 50% of patients treated with chemoradiation therapy [3]. Patients with inflammatory bowel diseases (IBDs), such as ulcerative colitis and Crohn's disease, have an increased risk for developing colitis-associated CRC [4]. IBDs are characterized by a chronic inflammatory state with an altered intestinal permeability and gut microbiota leading to a dysbiotic intestinal state [5]. These alterations and inflammation alter the normal gut microenvironment and contribute to the pathogenesis of CRC [6, 7]. Unresolved inflammation generates a microenvironment favorable for cellular transformation and the growth of cancer cells. Ulcerative colitis and Crohn's disease account for 10% to 15% of deaths in patients with CRC [8, 9]. In addition, increased consumption of a low-fiber diet lacking essential nutrients, alcohol/tobacco, red meat, a lack of physical activity [10], and obesity [11] increases the risk of CRC development. Furthermore, family history of CRC, the presence of precancerous CRC polyps, genetic syndromes such as lynch syndrome and familial adenomatous polyposis, and type 2 diabetes are other important risk factors that contribute to the development

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# Dysregulated FOXM1 signaling in the regulation of cancer stem cells

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ABSTRACT

Since the introduction of the cancer stem cell (CSC) paradigm, significant advances have been made in understanding the functional and biological plasticity of these elusive components in malignancies. Endowed with self-renewing abilities and multilineage differentiation potential, CSCs have emerged as cellular drivers of virtually all facets of tumor biology, including metastasis, tumor recurrence/relapse, and drug resistance. The functional and biological characteristics of CSCs, such as self-renewal, cell fate decisions, survival, proliferation, and differentiation are regulated by an array of extracellular factors, signaling pathways, and pluripotent transcriptional factors. Besides the well-characterized regulatory role of transcription factors OCT4, SOX2, NANOG, KLF4, and MYC in CSCs, evidence for the central role of Forkhead box transcription factor FOXM1 in the establishment, maintenance, and functions of CSCs is accumulating. Conventionally identified as a master regulator of the cell cycle, a comprehensive understanding of this molecule has revealed its multifarious oncogenic potential and uncovered its role in angiogenesis, invasion, migration, self-renewal, and drug resistance. This review compiles the large body of literature that has accumulated in recent years that provides evidence for the mechanisms by which FOXM1 expression promotes stemness in glioblastoma, breast, colon, ovarian, lung, hepatic, and pancreatic carcinomas. We have also compiled the data showing the association of stem cell mediators with FOXM1 using TCGA mRNA expression data. Further, the prognostic importance of FOXM1 and other stem cell markers is presented. The delineation of FOXM1-mediated regulation of CSCs can aid in the development of molecularly targeted pharmacological approaches directed at the selective eradication of CSCs in several human malignancies.

## 1. Introduction

There are more than 2500 proteins in humans thought to bind to chromatin to regulate replication, repair, unwinding, and transcription of DNA. A considerable number of these proteins (about 1500) function as transcription factors (TFs), characterized are proteins that bind to certain regulatory regions on the DNA helix to activate or inhibit transcription. The transcription process in all living beings leads to the fine and spatiotemporally controlled synthesis of ribonucleic acids and is initiated by extrinsic or intrinsic triggers through a signal transduction

*Abbreviations:* CSC, Cancer stem cell; TF, Transcription factor; Fox, Forkhead box; TNBC, Triple-negative breast cancer; BCSC, Breast cancer stem cell; BC, Breast cancer; CRC, Colorectal cancer; CCSC, Colorectal cancer stem cell; MnSOD, Manganese-dependent superoxide dismutase; MELK, Maternal embryonic leucine zipper kinase; EMT, Epithelial to mesenchymal transition; ESC, Embryonic stem cell; HCC, Hepatocellular carcinoma; ROS, Reactive oxygen species; LCSC, Liver cancer stem cell; HSC, Hepatic stellate cell; HGF, Hepatocyte growth factor; LGSOC, Low-grade serous ovarian carcinoma; HGSOC, High-grade serous ovarian carcinoma; OCSC, Ovarian cancer stem cell; ATRA, All-trans retinoic acid; OCSLC, Ovarian cancer stem-like cell; hCTR1, Human copper transporter 1; EOC, Epithelial ovarian cancer; NSCLC, Non-small cell lung cancer; SCLC, Small cell lung cancer; Lung CSC, Lung cancer stem cell; GBM, Glioblastoma; GSC, Glioma stem cell; PC, Pancreatic cancer; PCSC, Pancreatic cancer stem cell; PDAC, Pancreatic ductal adenocarcinoma; TAM, Tamoxifen; Hh, Hedgehog.

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RESEARCH ARTICLE

# Nomograms of human hippocampal volume shifted by polygenic scores

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**Abstract** Nomograms are important clinical tools applied widely in both developing and aging populations. They are generally constructed as normative models identifying cases as outliers to a distribution of healthy controls. Currently used normative models do not account for genetic heterogeneity. Hippocampal volume (HV) is a key endophenotype for many brain disorders. Here, we examine the impact of genetic adjustment on HV nomograms and the translational ability to detect dementia patients. Using imaging data from 35,686 healthy subjects aged 44–82 from the UK Biobank (UKB), we built HV nomograms using Gaussian process regression (GPR), which – compared to a previous method – extended the application age by 20 years, including dementia critical age ranges. Using HV polygenic scores (HV-PGS), we built genetically adjusted nomograms from participants stratified into the top and bottom 30% of HV-PGS. This shifted the nomograms in the expected directions by ~100 $mm^3$ (2.3% of the average HV), which equates to 3 years of normal aging for a person aged ~65. Clinical impact of genetically adjusted nomograms was investigated by comparing 818 subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database diagnosed as either cognitively normal (CN), having mild cognitive impairment (MCI) or Alzheimer's disease (AD) patients. While no significant change in the survival analysis was found for MCI-to-AD conversion, an average of 68% relative decrease was found in intra-diagnostic-group variance, highlighting the importance of genetic adjustment in untangling phenotypic heterogeneity.

## Editor's evaluation

This manuscript considers whether genetic information can improve the clinical utility of population norms derived from brain imaging data. The authors propose to incorporate polygenic scores into normative models of hippocampal volume to improve predictions of neurodegenerative disease. This approach is elegantly demonstrated in this manuscript and may be useful for clinical translation of population neuroimaging.

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## Introduction

Brain imaging genetics is a rapidly evolving area of neuroscience combining imaging, genetic, and clinical data to gain insight into normal and diseased brain morphology and function (***Shen and Thompson, 2020***). Normative modelling is an emerging method in neuroscience, aiming to identify

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# Human leukocyte antigen class II gene diversity tunes antibody repertoires to common pathogens

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Allelic diversity of human leukocyte antigen (HLA) class II genes may help maintain humoral immunity against infectious diseases. In this study, we investigated germline genetic variation in classical HLA class II genes and employed a systematic, unbiased approach to explore the relative contribution of this genetic variation in the antibody repertoire to various common pathogens. We leveraged a well-defined cohort of 800 adults representing the general Arab population in which genetic material is shared because of the high frequency of consanguineous unions. By applying a high-throughput method for large-scale antibody profiling to this well-defined cohort, we were able to dissect the overall effect of zygosity for classical HLA class II genes, as well as the effects associated with specific HLA class II alleles, haplotypes and genotypes, on the antimicrobial antibody repertoire breadth and antibody specificity with unprecedented resolution. Our population genetic studies revealed that zygosity of the classical HLA class II genes is a strong predictor of antibody responses to common human pathogens, suggesting that classical HLA class II gene heterozygosity confers a selective advantage. Moreover, we demonstrated that multiple HLA class II alleles can have additive effects on the antibody repertoire to common pathogens. We also identified associations of HLA-DRB1 genotypes with specific antigens. Our findings suggest that HLA class II gene polymorphisms confer specific humoral immunity against common pathogens, which may have contributed to the genetic diversity of HLA class II loci during hominine evolution.

KEYWORDS

**human antibody repertoires, microbial infection, phage immunoprecipitation sequencing, human leukocyte antigen, major histocompatibility complex, polymorphisms, allelic diversity, association study**

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# Metabolomics Profiling of Vitamin D Status in Relation to Dyslipidemia

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**Abstract:** Vitamin D deficiency is a global disorder associated with several chronic illnesses including dyslipidemia and metabolic syndrome. The impact of this association with both dyslipidemia and vitamin D deficiency on metabolomics profile is not yet fully understood. This study analyses the metabolomics and lipidomic signatures in relation to vitamin D status and dyslipidemia. Metabolomics data were collected from Qatar Biobank database and categorized into four groups based on vitamin D and dyslipidemia status. Metabolomics multivariate analysis was performed using the orthogonal partial least square discriminate analysis (OPLS-DA) whilst linear models were used to assess the per-metabolite association with each of the four dyslipidemia/vitamin D combination groups. Our results indicate a high prevalence of vitamin D deficiency among the younger age group, while dyslipidemia was more prominent in the older group. A significant alteration of metabolomics profile was observed among the dyslipidemic and vitamin D deficient individuals in comparison with control groups. These modifications reflected changes in some key pathways including ceramides, diacylglycerols, hemosylceramides, lysophospholipids, phosphatidylcholines, phosphatidylethanol amines, and sphingomyelins. Vitamin D deficiency and dyslipidemia have a deep impact on sphingomyelins profile. The modifications were noted at the level of ceramides and are likely to propagate through downstream pathways.

**Keywords:** vitamin D; 25-hydroxyvitamin D; dyslipidemia; metabolomics; lipidomics



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## 1. Introduction

Vitamin D deficiency (serum 25 dihydroxy vitamin D (25(OH)D) concentrations <12 ng/mL) is a worldwide health problem affecting approximately 1 billion individuals globally, with vitamin D insufficiency (<20 ng/mL) affecting 50% of the population. The elderly, obese individuals, nursing home residents, and hospitalized patients have the greatest rates of vitamin D deficiency [1,2]. In Qatar, Al-Dabhani et al. found that 64% of the 1205 individuals in their research cohort were vitamin D deficient and suffered vitamin-D-related morbidity [3].

In recent years, a growing body of epidemiological and experimental data has shown that low blood vitamin D levels are associated with a variety of metabolic illnesses, including dyslipidemia, obesity, type 2 diabetes, insulin resistance, and cardiovascular disease, including hypertension [4]. In a study by Jiang et al., it was revealed that low vitamin D levels were inversely associated with LDL and triglycerides levels, whereas higher vitamin D levels were linked to high HDL [5]. HDL is dubbed as the "good" cholesterol, tasked with extracting excess cholesterol from peripheral arteries and transferring it to the liver for elimination in a process known as reverse cholesterol transfer [6]. As a result, guidelines recommend lowering triglyceride and LDL levels while increasing HDL levels. The activities of dyslipidemia medications, which reduce triglyceride and LDL levels while boosting HDL levels, support these guidelines.

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*Article*

# Transcriptome Profile Identifies Actin as an Essential Regulator of Cardiac Myosin Binding Protein C3 Hypertrophic Cardiomyopathy in a Zebrafish Model

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**Abstract:** Variants in cardiac myosin-binding protein C (cMyBP-C) are the leading cause of inherited hypertrophic cardiomyopathy (HCM), demonstrating the key role that cMyBP-C plays in the heart's contractile machinery. To investigate the *c-MYBPC3* HCM-related cardiac impairment, we generated a zebrafish *mypbc3*-knockout model. These knockout zebrafish displayed significant morphological heart alterations related to a significant decrease in ventricular and atrial diameters at systolic and diastolic states at the larval stages. Immunofluorescence staining revealed significant hyperplasia in the mutant's total cardiac and ventricular cardiomyocytes. Although cardiac contractility was similar to the wild-type control, the ejection fraction was significantly increased in the *mypbc3* mutants. At later stages of larval development, the mutants demonstrated an early cardiac phenotype of myocardium remodeling, concurrent cardiomyocyte hyperplasia, and increased ejection fraction as critical processes in HCM initiation to counteract the increased ventricular myocardial wall stress. The examination of zebrafish adults showed a thickened ventricular cardiac wall with reduced heart rate, swimming speed, and endurance ability in both the *mypbc3* heterozygous and homozygous groups. Furthermore, heart transcriptome profiling showed a significant downregulation of the actin-filament-based process, indicating an impaired actin cytoskeleton organization as the main dysregulating factor associated with the early ventricular cardiac hypertrophy in the zebrafish *mypbc3* HCM model.

**Keywords:** hypertrophic cardiomyopathy; HCM; *c-MYBPC3*; actin; RNA seq; zebrafish knockout

## 1. Introduction

Hypertrophic cardiomyopathy (HCM) is one of the most common heritable cardiac conditions, with an estimated prevalence in the general population of >1:500 [1–3]. HCM is an archetypical single gene disorder with an autosomal dominant pattern of inheritance [4,5]. Patients usually present with fatigue, palpitations, dizziness, dyspnea, syncope, angina, and congestive heart failure. Clinical characteristics include left ventricular hypertrophy, diastolic dysfunction, outflow obstruction, and myocardial ischemia [6]. It is

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Review

# Natural products as chemo-radiation therapy sensitizers in cancers

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ABSTRACT

Cancer is a devastating disease and is the second leading cause of death worldwide. Surgery, chemotherapy (CT), and/or radiation therapy (RT) are the treatment of choice for most advanced tumors. Unfortunately, treatment failure due to intrinsic and acquired resistance to the current CT and RT is a significant challenge associated with poor patient prognosis. There is an urgent need to develop and identify agents that can sensitize tumor cells to chemo-radiation therapy (CRT) with minimal cytotoxicity to the healthy tissues. While many recent studies have identified the underlying molecular mechanisms and therapeutic targets for CRT failure, using small molecule inhibitors to chemo/radio sensitize tumors is associated with high toxicity and increased morbidity. Natural products have long been used as chemopreventive agents in many cancers. Combining many of these compounds with the standard chemotherapeutic agents or with RT has shown synergistic effects on cancer cell death and overall improvement in patient survival. Based on the available data, there is strong evidence that natural products have a robust therapeutic potential along with CRT and their well-known chemopreventive effects in many solid tumors. This review article reports updated literature on different natural products used as CT or RT sensitizers in many solid tumors. This is the first review discussing CT and RT sensitizers together in cancer.

## 1. Introduction

Cancer is a devastating disease and the 2nd cause of death worldwide. International Agency for Research on Cancer (IARC) expects 21.7 and 13 million incidences and deaths, respectively, in 2030 worldwide [1]. While surgery and chemotherapy (CT) and/or radiotherapy (RT) are the standard of care for most advanced tumors, intrinsic or acquired resistance to the CT or RT limits the efficacy and results in poor patient prognosis. Unsurprisingly, 80–90% of cancer-associated deaths are attributed to drug resistance and the development of refractory tumors [2]. Though the underlying mechanisms of resistance can be multifactorial and completely unknown, recent molecular studies suggest the involvement of deregulated drug targets, pro-survival and anti-apoptotic signaling pathways [3]. In addition, most current chemotherapeutic drugs are toxic to the normal tissues, including the gastrointestinal (GI) tract, heart, bone marrow, lungs, kidneys, etc. [4]. Most importantly, organ failure due to these cytotoxic drugs is a frequent cause of cancer-related deaths [4]. These limitations of the chemotherapeutic drugs have prompted researchers to develop small molecular inhibitors for targeted therapies, but unfortunately, their

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# At-home blood collection and stabilization in high temperature climates using *home*RNA

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Expanding whole blood sample collection for transcriptome analysis beyond traditional phlebotomy clinics will open new frontiers for remote immune research and telemedicine. Determining the stability of RNA in blood samples exposed to high ambient temperatures (>30°C) is necessary for deploying home-sampling in settings with elevated temperatures (e.g., studying physiological response to natural disasters that occur in warm locations or in the summer). Recently, we have developed *home*RNA, a technology that allows for self-blood sampling and RNA stabilization remotely. *home*RNA consists of a lancet-based blood collection device, the Tasso-SST™ which collects up to 0.5 ml of blood from the upper arm, and a custom-built stabilization transfer tube containing RNA*later*™. In this study, we investigated the robustness of our *home*RNA kit in high temperature settings via two small pilot studies in Doha, Qatar (no. participants = 8), and the Western and South Central USA during the summer of 2021, which included a heatwave of unusually high temperatures in some locations (no. participants = 11). Samples collected from participants in Doha were subjected to rapid external temperature fluctuations from being moved to and from air-conditioned areas and extreme heat environments (up to 41°C external temperature during brief temperature spikes). In the USA pilot study, regions varied in outdoor temperature highs (between 25°C and 43.4°C). All samples that returned a RNA integrity number (RIN) value from the Doha, Qatar group had a RIN ≥7.0, a typical integrity threshold for downstream transcriptomics analysis. RIN values for the Western and South Central USA samples ($n$ = 12 samples) ranged from 6.9–8.7 with 9 out of 12 samples reporting RINs ≥7.0. Overall, our pilot data suggest that *home*RNA can be used in some regions that experience elevated temperatures, opening up new geographical frontiers in disseminated transcriptome analysis for applications critical to telemedicine, global health, and expanded clinical research. Further studies, including our ongoing work in Qatar, USA, and Thailand, will continue to test the robustness of *home*RNA.

KEYWORDS

home blood sampling, personalized medicine, RNA stabilization, high temperature sampling, global health

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REVIEW

# The molecular genetics of human appendicular skeleton

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**Abstract**
Disorders that result from de-arrangement of growth, development and/or differentiation of the appendages (limbs and digit) are collectively called as inherited abnormalities of human appendicular skeleton. The bones of appendicular skeleton have central role in locomotion and movement. The different types of appendicular skeletal abnormalities are well described in the report of "*Nosology and Classification of Genetic skeletal disorders*: *2019 Revision*". In the current article, we intend to present the embryology, developmental pathways, disorders and the molecular genetics of the appendicular skeletal malformations. We mainly focused on the polydactyly, syndactyly, brachydactyly, split-hand–foot malformation and clubfoot disorders. To our knowledge, only nine genes of polydactyly, five genes of split-hand–foot malformation, nine genes for syndactyly, eight genes for brachydactyly and only single gene for clubfoot have been identified to be involved in disease pathophysiology. The current molecular genetic data will help life sciences researchers working on the rare skeletal disorders. Moreover, the aim of present systematic review is to gather the published knowledge on molecular genetics of appendicular skeleton, which would help in genetic counseling and molecular diagnosis.

**Keywords** Appendicular skeleton · Skeleton pathways · Molecular genetics · Mutations · Databases

## Human skeleton

The skeleton of an adult human is composed of two hundred and thirteen (213) bones, apart from the sesamoid bones (Standring 2015). These include 74 axial skeleton bones, 126 appendicular skeleton bones and 6 auditory ossicle bones. Bone modeling is a continuous process that happens throughout the life of an individual. Bone modeling helps to adjust the bones according to the bio-mechanical forces, removes damaged bones tissues and replaces it with fresh mechanically stronger bone to maintain its strength. There are four common bone categories, namely short bones, long bones, irregular bones and flat bones. Long bones include clavicles, radii, humeri, ulnae, femurs, metacarpals, tibiae, metatarsals, phalanges and fibulae. Short bones include carpal bones and tarsal bones, sesamoid bones and patellae. Flat bones consist of multiple bones of the cranium and the scapulae, mandible, ribs and sternum. The irregular bones include vertebrae, coccyx, hyoid bone and sacrum. Apart from providing structural strength, the skeleton performs several important functions such as providing muscles levers to enable locomotion and movement, protecting significant interior organs and structures, preservation of mineral homeostasis and acid–base balance, acting as a growth factors and cytokines reservoir and providing the medium for hematopoiesis inside the marrow spaces (Taichman 2005).

The objective of present systematic review is to gather the published literature on molecular genetics and associated pathways of appendicular skeleton, with the intention of broad application in research, genetic counseling and molecular diagnosis. The current report comprehensive explained the different types of appendicular skeletal disorders, their associated pathways, and molecular genetics. The present systematic review provides a consolidated knowledge to researchers and healthcare providers to understand the biology of appendicular skeleton and its development.

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# MTG8 interacts with LHX6 to specify cortical interneuron subtype identity

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Cortical interneurons originating in the embryonic medial ganglionic eminence (MGE) diverge into a range of different subtypes found in the adult mouse cerebral cortex. The mechanisms underlying this divergence and the timing when subtype identity is set up remain unclear. We identify the highly conserved transcriptional co-factor MTG8 as being pivotal in the development of a large subset of MGE cortical interneurons that co-expresses Somatostatin (SST) and Neuropeptide Y (NPY). MTG8 interacts with the pan-MGE transcription factor LHX6 and together the two factors are sufficient to promote expression of critical cortical interneuron subtype identity genes. The SST-NPY cortical interneuron fate is initiated early, well before interneurons migrate into the cortex, demonstrating an early onset specification program. Our findings suggest that transcriptional co-factors and modifiers of generic lineage specification programs may hold the key to the emergence of cortical interneuron heterogeneity from the embryonic telencephalic germinal zones.

A large diversity of cortical GABAergic interneurons has been identified in the mammalian cerebral cortex on the basis of molecular, electrophysiological, morphological and connectivity signatures[1–5]. The development of this diversity begins early during embryogenesis when cortical interneurons are specified from subcortical precursors[6,7]. Although mature gene networks and epigenetic signatures become evident only when interneurons settle in the cortex[8], specification starts early, and embryonic gene expression in newly differentiated neurons reflects cortical interneuron mature identities[9]. Hence, genetic programs that instruct interneuron fates initiate early but unfold gradually subject to intrinsic and extrinsic influences[10,11].

SST- and Parvalbumin (PV)-expressing cortical interneurons are the two major classes of interneurons that are generated from the MGE[12]. More than 15 different SST and PV interneuron subtypes have been identified to date and yet we lack all knowledge as to how this fine diversity is generated[4,13]. NKX2-1 and its downstream target, LHX6, constitute the core molecular cascade governing the onset of MGE-interneuron development[14,15]. LHX6 is expressed in the entire MGE cortical interneuron lineage at all prenatal and postnatal stages and is required for specification, migration, laminar distribution and differentiation of MGE interneurons[16–18]. How LHX6 performs these diverse functions remains unknown.

*Myeloid translocation genes* (*Mtg*) encode non-DNA binding transcriptional regulators that associate with DNA-binding factors to recruit regulatory protein complexes to target loci[19,20]. They are so named because they are frequent targets of translocation in acute myeloid leukaemia[20]. MTG proteins are best known as transcriptional co-repressors with high networking capacity that regulate cell fate decisions and differentiation in different systems[21–23]. Three family members have been identified to date: *Mtg8* (*Runx1t1*), *Mtg16* (*Cbfa2t3*)

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PLOS ONE

RESEARCH ARTICLE

# HIV-1 Vpr suppresses expression of the thiazide-sensitive sodium chloride co-transporter in the distal convoluted tubule

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## Abstract

HIV-associated nephropathy (HIVAN) impairs functions of both glomeruli and tubules. Attention has been previously focused on the HIVAN glomerulopathy. Tubular injury has drawn increased attention because sodium wasting is common in hospitalized HIV/AIDS patients. We used viral protein R (Vpr)-transgenic mice to investigate the mechanisms whereby Vpr contributes to urinary sodium wasting. In phosphoenolpyruvate carboxykinase promoter-driven Vpr-transgenic mice, *in situ* hybridization showed that Vpr mRNA was expressed in all nephron segments, including the distal convoluted tubule. Vpr-transgenic mice, compared with wild-type littermates, markedly increased urinary sodium excretion, despite similar plasma renin activity and aldosterone levels. Kidneys from Vpr-transgenic mice also markedly reduced protein abundance of the $Na^+$-$Cl^-$ cotransporter (NCC), while mineralocorticoid receptor (MR) protein expression level was unchanged. In African green monkey kidney cells, Vpr abrogated the aldosterone-mediated stimulation of MR transcriptional activity. Gene expression of *Slc12a3* (NCC) in Vpr-transgenic mice was significantly lower compared with wild-type mice, assessed by both qRT-PCR and RNAScope *in situ* hybridization analysis. Chromatin immunoprecipitation assays identified multiple MR response elements (MRE), located from 5 kb upstream of the transcription start site and

genes

MDPI

*Article*

# Exome Sequencing Identified Molecular Determinants of Retinal Dystrophies in Nine Consanguineous Pakistani Families

**Raeesa Tehreem [1], Iris Chen [2], Mudassar Raza Shah [1], Yumei Li [2], Muzammil Ahmad Khan [3,4], Kiran Afshan [1], Rui Chen [2,*] and Sabika Firasat [1,*]**

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**Abstract:** Inherited retinal dystrophies (IRDs) are a heterogeneous group of degenerative disorders of the retina. Retinitis Pigmentosa (RP) is a common type of IRD that causes night blindness and loss of peripheral vision and may progress to blindness. Mutations in more than 300 genes have been associated with syndromic and non-syndromic IRDs. Recessive forms are more frequent in populations where endogamy is a social preference, such as Pakistan. The aim of this study was to identify molecular determinants of IRDs with the common presentation of night blindness in consanguineous Pakistani families. This study included nine consanguineous IRD-affected families that presented autosomal recessive inheritance of the night blindness phenotype. DNA was extracted from blood samples. Targeted exome sequencing of 344 known genes for retinal dystrophies was performed. Screening of nine affected families revealed two novel (c.5571_5576delinsCTAGATand c.471dup in *EYS* and *SPATA7* genes, respectively) and six reported pathogenic mutations (c.304C>A, c.187C>T, c.1560C>A, c.547C>T, c.109del and c.9911_11550del in *PDE6A*, *USH2A*, USH2A, *NMNAT1*, *PAX6* and *ALMS1* genes, respectively) segregating with disease phenotype in each respective family. Molecular determinants of hereditary retinal dystrophies were identified in all screened families. Identification of novel variants aid future diagnosis of retinal dystrophies and help to provide genetic counseling to affected families.

**Keywords:** retinaldystrophies; night blindness; homozygous sequence variants; autosomal recessive



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## 1. Introduction

Inherited retinal dystrophies (IRDs) are degenerative eye disorders causing substantial loss of vision and even blindness [1]. The most common inheritable retinal dystrophy is retinitis pigmentosa (RP), which is characterized by the degradation of photoreceptors, predominantly rods and secondarily tightly packed cones [2]. In the initial stage of disease, night vision is reduced, followed by loss of peripheral vision in the diseased individuals [3]. Different values of prevalence are reported from various regions worldwide; from 1:372 in rural regions of South India [4] to 1:9000 in Korea [5]. RP can be present in both non-syndromic and syndromic forms. In non-syndromic forms, it can be inherited in autosomal pattern (dominant/recessive), X-linked pattern (dominant/recessive), mitochondrial inheritance or sporadic cases [6]. Syndromic forms of RP such as Bardet–Biedl syndrome (MIM no. 209900) and Usher syndrome (MIM no. 276901) are associated with extra ocular abnormalities and are reported in almost 20–30% cases [3].

Significant overlap at both the clinical and molecular level is observed between different forms of IRDs. For example, early onset RP can be detected at the age of 2 years and could overlap with Leber's congenital amaurosis (LCA) (MIM # 204000) [2], but in

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REVIEW Open Access

# The potential impact of a probiotic: *Akkermansia muciniphila* in the regulation of blood pressure—the current facts and evidence

Arun Prasath Lakshmanan[1*†], Selvasankar Murugesan[2†], Souhaila Al Khodor[2] and Annalisa Terranegra[1*]

**Abstract**

*Akkermansia muciniphila* (*A. muciniphila*) is present in the human gut microbiota from infancy and gradually increases in adulthood. The potential impact of the abundance of *A. muciniphila* has been studied in major cardiovascular diseases including elevated blood pressure or hypertension (HTN). HTN is a major factor in premature death worldwide, and approximately 1.28 billion adults aged 30–79 years have hypertension. *A. muciniphila* is being considered a next-generation probiotic and though numerous studies had highlighted the positive role of *A. muciniphila* in lowering/controlling the HTN, however, few studies had highlighted the negative impact of increased abundance of *A. muciniphila* in the management of HTN. Thus, in the review, we aimed to discuss the current facts, evidence, and controversy about the role of A. *muciniphila* in the pathophysiology of HTN and its potential effect on HTN management/regulation, which could be beneficial in identifying the drug target for the management of HTN.

**Keywords:** *Akkermansia muciniphila*, Hypertension, Gut microbiome, Metagenomic, Blood pressure, Gut microbiota

## Introduction

*Akkermansia* spp., belong to the Verrucomicrobia family, with only two species identified so far, namely *Akkermansia muciniphila (A. muciniphila)* and *Akkermansia glycaniphila* [1, 2]. Both species are considered intestinal mucin-degrading bacterium; the former was initially isolated from the fecal samples of healthy Caucasian females in 2004, whereas the latter was isolated from fecal samples of reticulated python, *Malayopython reticulatus* in 2016 [1, 2]. *A. muciniphila* is an oval-shaped, non-motile, and gram-negative anaerobic bacteria, that grows well with an optimum temperature of 37 °C and pH of 6.5 [1], and it is present in wild animals, mice, hamsters, and humans [3]. Caputo et al. successfully sequenced *A. muciniphila*, directly from human stool samples using the whole-genome assembly method [4], and the abundance level of *A. muciniphila* in the human feces sample is approximately 3–4%. In rare conditions, the abundance level can increase up to 5% [5]. *A. muciniphila* is considered a potential probiotic due to its nature that can effectively use the gastrointestinal tract (GI) mucin [6] and possesses a unique survival mechanism, that is, the degradation of gastrointestinal mucin from the host causing the release of carbon and nitrogen sources for its survival [1, 7]. Also, its abundance level is modulated by dietary patterns and other changes in the mucin level [8]. In addition, it promotes the growth of other bacteria through a cross-feeding mechanism, mainly releasing amino acids and sugars during the GI mucin degradation process [8]. Its role has been studied in major diseases,

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RESEARCH Open Access

# Immune-related 3-lncRNA signature with prognostic connotation in a multi-cancer setting

Shimaa Sherif[1,2†], Raghvendra Mall[3,4†], Hossam Almeer[3], Adviti Naik[5], Abdulaziz Al Homaid[3], Remy Thomas[5], Jessica Roelands[2,6], Sathiya Narayanan[2], Mahmoud Gasim Mohamed[7], Shahinaz Bedri[8], Salha Bujassoum Al-Bader[9], Kulsoom Junejo[10], Davide Bedognetti[1,2], Wouter Hendrickx[1,2*] and Julie Decock[1,5*]

## Abstract

**Background:** Advances in our understanding of the tumor microenvironment have radically changed the cancer field, highlighting the emerging need for biomarkers of an active, favorable tumor immune phenotype to aid treatment stratification and clinical prognostication. Numerous immune-related gene signatures have been defined; however, their prognostic value is often limited to one or few cancer types. Moreover, the area of non-coding RNA as biomarkers remains largely unexplored although their number and biological roles are rapidly expanding.

**Methods:** We developed a multi-step process to identify immune-related long non-coding RNA signatures with prognostic connotation in multiple TCGA solid cancer datasets.

**Results:** Using the breast cancer dataset as a discovery cohort we found 2988 differentially expressed lncRNAs between immune favorable and unfavorable tumors, as defined by the immunologic constant of rejection (ICR) gene signature. Mapping of the lncRNAs to a coding-non-coding network identified 127 proxy protein-coding genes that are enriched in immune-related diseases and functions. Next, we defined two distinct 20-lncRNA prognostic signatures that show a stronger effect on overall survival than the ICR signature in multiple solid cancers. Furthermore, we found a 3 lncRNA signature that demonstrated prognostic significance across 5 solid cancer types with a stronger association with clinical outcome than ICR. Moreover, this 3 lncRNA signature showed additional prognostic significance in uterine corpus endometrial carcinoma and cervical squamous cell carcinoma and endocervical adenocarcinoma as compared to ICR.

**Conclusion:** We identified an immune-related 3-lncRNA signature with prognostic connotation in multiple solid cancer types which performed equally well and in some cases better than the 20-gene ICR signature, indicating that it could be used as a minimal informative signature for clinical implementation.

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# Current and emerging biomarkers in ovarian cancer diagnosis; CA125 and beyond

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## Abstract

Ovarian cancer (OC) is one of the most common causes of cancer-related death in women worldwide. Its five-year survival rates are worse than the two most common gynecological cancers, cervical and endometrial. This is because it is asymptomatic in the early stages and usually detected in the advanced metastasized stage. Thus, survival is increasingly dependent on timely diagnosis. The delay in detection is contributed partly by the occurrence of non-specific clinical symptoms in the early stages and the lack of effective biomarkers and detection approaches. This underlines the need for biomarker identification and clinical validation, enabling earlier diagnosis, effective prognosis, and response to therapy. Apart from the traditional diagnostic biomarkers for OC, several new biomarkers have been delineated using advanced high-throughput molecular approaches in recent years. They are currently being clinically evaluated for their true diagnostic potential. In this chapter, we document the commonly utilized traditional screening markers and recently identified emerging biomarkers in OC diagnosis, focusing on secretory and protein biomarkers. We also briefly reviewed the recent advances and prospects in OC diagnosis.

**Keywords:** Biomarkers; Cancer antigens; Cell-free DNA; Circulating tumor cells; Liquid biopsy; Multiplexed assays; Ovarian cancer; Secretory proteins.

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# Modulation of gut microbiota: The effects of a fruits and vegetables supplement

Arun Prasath Lakshmanan[1†], Alessandra Mingione[2†], Francesca Pivari[3†], Elena Dogliotti[4], Caterina Brasacchio[3], Selvasankar Murugesan[5], Daniele Cusi[6,7], Monica Lazzaroni[8], Laura Soldati[3‡] and Annalisa Terranegra[1*‡]

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The consumption of an optimal amount of fruits and vegetables is known to improve physical fitness and physiological body functions. Healthy eating habits, including intake of fruits and vegetables, can modify gut microbiota. This study aimed to demonstrate the effectiveness of a formulated fruit and vegetable supplement (FVS) in modulating the antioxidant capacity and the gut microbiota composition. We enrolled 30 healthy volunteer subjects, matched for age, gender, BMI, and smoking habits, and randomized them into the FVS and the placebo (PLA) groups. Among the serum vitamins, the folic acid level was significantly higher ($p$ = 0.001) in the FVS group than in the PLA group, whereas the vitamin B2 level was significantly higher in the PLA group than in the FVS group ($p$ = 0.028). The antioxidant capacity, measured by using the oxygen radical absorbance capacity (ORAC) method, was also slightly higher in the FVS group than in the PLA group but did not reach statistical significance. The dietary intake, assessed by 24-h recalls, did not show any significant changes after the supplementation in both the groups. The gut microbiome composition, measured by 16S rDNA sequencing, showed no difference in both alpha and beta diversities, whereas the LEfse analysis revealed a microbial shift after the treatment, with a decreased abundance of the genus *Ruminococcus* from the Lachnospiraceae family ($p$ = 0.009), and the unclassified genus from the family Erysipelotrichaceae (UC36, $p$ = 0.003) in the FVS group compared with the PLA group (confirmed by SIAMCAT analysis, AUC = 74.1%). With a minor effect, the genus *Faecalibacterium* and unclassified genus and family from the order Lactobacillales (UC31) were also increased in the FVS group compared with the PLA group ($p$ = 0.0474, $p$ = 0.0352, respectively). SCFA measurement by gas chromatography–mass spectrometry showed an increased level of 2-methylbutyrate in the FVS group compared with the PLA group ($p$ = 0.0385). Finally, the Spearman correlation analysis showed

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Review

# A novel homozygous variant in homologous recombination repair gene *ZSWIM7* causes azoospermia in males and primary ovarian insufficiency in females

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ABSTRACT

Infertility is a common, clinically heterogeneous reproductive disorder worldwide with a prevalence of about 15%. To date about eighty genes have been discovered to cause non-syndromic infertility, affecting males and females equally, though traditionally the genetic analysis of each group has been conducted separately. Here, we report the clinical and genetic characterization of a consanguineous family of Pakistani origin with multiple individuals, including male and female, affected with infertility. Males exhibited non-obstructive azoospermia whereas females had primary ovarian insufficiency.

Whole exome sequencing revealed a missense variant [c.176C > T, p. (Ser59Leu)] in the *ZSWIM7* gene which functions in homologous recombination repair. The variant was found in a homozygous form in all affected males and females. To our knowledge, this is the first family that has individuals affected with infertility in both sexes. This point to the utility of large consanguineous families with multiple affected siblings to reveal joint mechanisms affecting human reproduction.

## 1. Introduction

Infertility is a common reproductive disorder affecting 15% of couples worldwide where 50% of infertile individuals are males (Vander Borght and Wyns, 2018). Male infertility is caused by disruption of a spermatogenic process which results in defects in the shape, number, and function of spermatozoa. Female infertility may be caused by ovulation defects due to hormonal imbalances, autoimmune response, or premature loss of eggs. The prevalence of infertility varies in different regions of the world. Recently, a study revealed 24.6% female infertility in the Chinese female population which constituted 6.54% primary infertility and 18.04% secondary infertility (Liang et al., 2021). Primary ovarian insufficiency (POI) is a compelling cause of infertility affecting 1% women (Eshre Guideline Group on POI et al., 2016). The defective ovaries result in abnormal development of the resting follicles leading to primary amenorrhea (Nelson, 2009; De Vos et al., 2010). Primary amenorrhea is a key feature which is defined as the absence of menarche at the age of puberty. It is differentiated from secondary amenorrhea which is the absence of three or more consecutive periods after menarche.

Infertility is a genetically heterogeneous disorder with more than eighty genes that have been associated with nonsyndromic infertility (Matzuk and Lamb, 2008; Alhathal et al., 2020; Chen et al., 2020). The genes from a wide variety of molecular and cellular pathways have been demonstrated to play essential roles in driving and coordinating the cellular differentiation of spermatogonia into spermatozoa (Oud et al.,

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# Immune Profiling and Multiplexed Label-Free Detection of 2D MXenes by Mass Cytometry and High-Dimensional Imaging

*Laura Fusco, Arianna Gazzi, Christopher E. Shuck, Marco Orecchioni, Dafne Alberti, Sènan Mickael D'Almeida, Darawan Rinchai, Eiman Ahmed, Ofer Elhanani, Martina Rauner, Barbara Zavan, Jean-Charles Grivel, Leeat Keren, Giulia Pasqual, Davide Bedognetti, Klaus Ley, Yury Gogotsi,* and Lucia Gemma Delogu**

**There is a critical unmet need to detect and image 2D materials within single cells and tissues while surveying a high degree of information from single cells. Here, a versatile multiplexed label-free single-cell detection strategy is proposed based on single-cell mass cytometry by time-of-flight (CyTOF) and ion-beam imaging by time-of-flight (MIBI-TOF). This strategy, "Label-free sINgle-cell tracKing of 2D matErials by mass cytometry and MIBI-TOF Design" (LINKED), enables nanomaterial detection and simultaneous measurement of multiple cell and tissue features. As a proof of concept, a set of 2D materials, transition metal carbides, nitrides, and carbonitrides (MXenes), is selected to ensure mass detection within the cytometry range while avoiding overlap with more than 70 currently available tags, each able to survey multiple biological parameters. First, their detection and quantification in 15 primary human immune cell subpopulations are demonstrated. Together with the detection, mass cytometry is used to capture several biological aspects of MXenes, such as their biocompatibility and cytokine production after their uptake. Through enzymatic labeling, MXenes' mediation of cell–cell interactions is simultaneously evaluated. In vivo biodistribution experiments using a mixture of MXenes in mice confirm the versatility of the detection strategy and reveal MXene accumulation in the liver, blood, spleen, lungs, and relative immune cell subtypes. Finally, MIBI-TOF is applied to detect MXenes in different organs revealing their spatial distribution. The label-free detection of 2D materials by mass cytometry at the single-cell level, on multiple cell subpopulations and in multiple organs simultaneously, will enable exciting new opportunities in biomedicine.**

## 1. Introduction

The ability to track, detect, and quantitatively measure nanomaterials in cells and tissues has driven their increasing exploitation in biomedicine. The development of label-free, high-resolution, and high-dimensional approaches that simultaneously visualize 2D) materials in multiple cell types, thus enabling insight into cell functions and interactions, together with their spatial localization in tissues, will be crucial for translating nanomaterials to clinical applications.

Transition metal carbides, nitrides, and carbonitrides (MXenes)[1,2] are emergent 2D materials with a wide variety of structures and compositions.[3,4] Although the most studied MXene is $Ti_3C_2$, more than 30 stoichiometric compositions and at least 20 solid solutions have been reported. The surfaces of those 2D sheets are covered by functional groups, written as $T_x$. These groups primarily comprise O, OH and F, and thus are hydrophilic and easily dispersible in water and physiologic media. Because most MXenes have been shown to have biocompatibility and no cytotoxicity, they have been widely

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THE EMBO JOURNAL

# Loss of ribonuclease *DIS3* hampers genome integrity in myeloma by disrupting DNA:RNA hybrid metabolism

Ilaria Gritti[1], Veronica Basso[2], Darawan Rinchai[3], Federica Corigliano[1], Silvia Pivetti[1], Marco Gaviraghi[1], Dalia Rosano[1], Davide Mazza[4], Sara Barozzi[5], Marco Roncador[6,7], Giovanni Parmigiani[6,7], Gaelle Legube[8], Dario Parazzoli[5], Davide Cittaro[9], Davide Bedognetti[3,10], Anna Mondino[2], Simona Segalla[1,*] & Giovanni Tonon[1,9,11,**]

## Abstract

**The ribonuclease *DIS3* is one of the most frequently mutated genes in the hematological cancer multiple myeloma, yet the basis of its tumor suppressor function in this disease remains unclear. Herein, exploiting the TCGA dataset, we found that DIS3 plays a prominent role in the DNA damage response. DIS3 inactivation causes genomic instability by increasing mutational load, and a pervasive accumulation of DNA:RNA hybrids that induces genomic DNA double-strand breaks (DSBs). DNA:RNA hybrid accumulation also prevents binding of the homologous recombination (HR) machinery to double-strand breaks, hampering DSB repair. DIS3-inactivated cells become sensitive to PARP inhibitors, suggestive of a defect in homologous recombination repair. Accordingly, multiple myeloma patient cells mutated for *DIS3* harbor an increased mutational burden and a pervasive overexpression of pro-inflammatory interferon, correlating with the accumulation of DNA:RNA hybrids. We propose *DIS3* loss in myeloma to be a driving force for tumorigenesis via DNA:RNA hybrid-dependent enhanced genome instability and increased mutational rate. At the same time, *DIS3* loss represents a liability that might be therapeutically exploited in patients whose cancer cells harbor *DIS3* mutations.**

**Keywords** DNA damage repair; DNA:RNA Hybrids; interferon; multiple myeloma; R-loops

**Subject Categories** Cancer; DNA Replication, Recombination & Repair; RNA Biology

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## Introduction

DNA:RNA hybrids are structures where an RNA transcript hybridizes with the DNA template, leaving the nontemplate DNA single-stranded. The resulting DNA:RNA hybrid and the displaced single-stranded DNA are collectively called R-loop (Sanz *et al*, 2016). DNA:RNA hybrids mostly arise as RNA polymerases progress through the genes during transcription, by the rehybridization of the nascent RNA to the template DNA strand. Genome-wide mapping experiments have revealed that the formation of DNA:RNA hybrids is diffuse, occupying up to 5% of mammalian genomes (Sanz *et al*, 2016). R-loops impact fundamental cellular functions, such as the regulation of gene expression (Ginno *et al*, 2012; Chédin, 2016) and transcriptional termination (Skourti-Stathaki & Proudfoot, 2014). Paradoxically, despite their broad involvement in many biological functions, when unbridled, they can also induce DNA damage and genome instability (Santos-Pereira & Aguilera, 2015). Cells have evolved different mechanisms to regulate DNA:RNA hybrid levels, based on the swift removal of the RNA

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*Molecular Sciences*

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*Article*

# Correlation of Immunological and Histopathological Features with Gene Expression-Based Classifiers in Colon Cancer Patients

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**Abstract:** The purpose of this study was to evaluate the association between four distinct histopathological features: (1) tumor infiltrating lymphocytes, (2) mucinous differentiation, (3) tumor-stroma ratio, plus (4) tumor budding and two gene expression-based classifiers—(1) consensus molecular subtypes (CMS) plus (2) colorectal cancer intrinsic subtypes (CRIS). All four histopathological features were retrospectively scored on hematoxylin and eosin sections of the most invasive part of the primary tumor in 218 stage II and III colon cancer patients from two independent cohorts (AMC-AJCC-90 and AC-ICAM). RNA-based CMS and CRIS assignments were independently obtained for all patients. Contingency tables were constructed and a $\chi 2$ test was used to test for statistical significance. Odds ratios with 95% confidence intervals were calculated. The presence of tumor infiltrating lymphocytes and a mucinous phenotype (>50% mucinous surface area) were strongly correlated with CMS1 ($p < 0.001$ and $p = 0.008$) and CRIS-A ($p = 0.006$ and $p < 0.001$). The presence of mucus ($\geq$ 10%) was associated with CMS3: mucus was present in 64.1% of all CMS3 tumors ($p < 0.001$). Although a clear association between tumor-stroma ratio and CMS4 was established in this study ($p = 0.006$), still 32 out of 61 (52.5%) CMS4 tumors were scored as stroma-low, indicating that CMS4 tumors cannot be identified solely based on stromal content. Higher budding counts were seen in CMS4 and CRIS-B tumors ($p = 0.045$ and $p = 0.046$). No other associations of the measured parameters were seen for any of the other CRIS subtypes. Our analysis revealed clear associations between histopathologic features and CMS or CRIS subtypes. However, identification of distinct molecular subtypes solely based on histopathology proved to be infeasible. Combining both molecular and morphologic features could potentially improve patient stratification.

**Keywords:** colon cancer; histopathology; consensus molecular subtypes; CRC intrinsic subtypes; tumor infiltrating lymphocytes; mucinous adenocarcinoma; tumor-stroma ratio; tumor budding

## 1. Introduction

Colon cancer (CC) is a complex and heterogeneous disease with significant variation in therapy response and clinical outcome. The tumor-node-metastasis (TNM) classification, based on tumor extension and invasion, provides prognostic information and is currently

# Vaginal microbiome: considerations for reproductive health

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PMID: 36314380 DOI: 10.2217/fmb-2022-0112

## Abstract

The microbial communities are an indispensable part of the human defense system and coexist with humans as symbionts, contributing to the metabolic functions and immune defense against pathogens. An ecologically stable vaginal microbiota is dominated by *Lactobacillus* species, which plays an important role in the prevention of genital infections by controlling the vaginal pH, reducing glycogen to lactic acid, and stimulating bacteriocins and hydrogen peroxide. In contrast, an abnormal vaginal microbial composition is associated with an increased risk of bacterial vaginosis, trichomoniasis, sexually transmitted diseases, preterm labor and other birth defects. This microbial diversity is affected by race, ethnicity, pregnancy, hormonal changes, sexual activities, hygiene practices and other conditions. In the present review, we discuss the changes in the microbial community of the vaginal region at different stages of a female's life cycle and its influence on her reproductive health and pathological conditions.

**Keywords:** Lactobacillus; bacterial vaginosis; preterm birth; vaginal microbiome.

REVIEW

# Role of RAS signaling in ovarian cancer [version 1; peer review: 2 approved]

Lubna Therachiyil[1,2], Anjana Anand[1], Abdullah Azmi[1], Ajaz Bhat[3], Hesham M. Korashy[2], Shahab Uddin[1]

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## Abstract

The RAS family of proteins is among the most frequently mutated genes in human malignancies. In ovarian cancer (OC), the most lethal gynecological malignancy, *RAS*, especially *KRAS* mutational status at codons 12, 13, and 61, ranges from 6–65% spanning different histotypes. Normally RAS regulates several signaling pathways involved in a myriad of cellular signaling cascades mediating numerous cellular processes like cell proliferation, differentiation, invasion, and death. Aberrant activation of RAS leads to uncontrolled induction of several downstream signaling pathways such as RAF-1/MAPK (mitogen-activated protein kinase), PI3K phosphoinositide-3 kinase (PI3K)/AKT, RalGEFs, Rac/Rho, BRAF (v-Raf murine sarcoma viral oncogene homolog B), MEK1 (mitogen-activated protein kinase kinase 1), ERK (extracellular signal-regulated kinase), PKB (protein kinase B) and PKC (protein kinase C) involved in cell proliferation as well as maintenance pathways thereby driving tumorigenesis and cancer cell propagation. *KRAS* mutation is also known to be a biomarker for poor outcome and chemoresistance in OC. As a malignancy with several histotypes showing varying histopathological characteristics, we focus on reviewing recent literature showcasing the involvement of oncogenic *RAS* in mediating carcinogenesis and chemoresistance in OC and its subtypes.

## Keywords

Ovarian cancers, RAS, Oncogene, mutation, cell signaling

This article is included in the Targeting the KRAS Mutation collection.

**Open Peer Review**

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**Annie John**, United Arab Emirates University, Al Ain, United Arab Emirates

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cancers

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# Guggulsterone Induces Apoptosis in Multiple Myeloma Cells by Targeting High Mobility Group Box 1 via Janus Activated Kinase/Signal Transducer and Activator of Transcription Pathway

**Sabah Akhtar [1], Lubna Zarif [1,2], Shilpa Kuttikrishnan [1,3], Kirti S. Prabhu [1], Kalyani Patil [1], Sabah Nisar [4], Haissam Abou-Saleh [2,5], Maysaloun Merhi [6], Said Dermime [6], Ajaz A. Bhat [4] and Shahab Uddin [1,7,8,*]**

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**Simple Summary:** Multiple myeloma (MM) is a cancer of white blood cells known as plasma cells. It is hard to treat cancer, thus requires new treatments. Herein, a plant extracted compound, guggulsterone (GS), has been investigated for its anticancer activity in MM cells. The results from this study revealed that GS could be used for the effective treatment of MM due to its ability to cause cell death in MM cells. It exhibits anticancer activity itself and also increases the effectiveness of other drugs when combined. Therefore, it could be further investigated for its possible utilization in clinics to treat MM patients.

**Abstract:** Multiple myeloma (MM) is a hematological disorder characterized by the abnormal expansion of plasma cells in the bone marrow. Despite great advances over the past three decades in discovering the efficacious therapies for MM, the disease remains incurable for most patients owing to emergence of drug-resistant cancerous cells. Guggulsterone (GS), a phytosteroid, extracted from the gum resin of guggul plant, has displayed various anticancer activities in vitro and in vivo; however, the molecular mechanisms of its anticancer activity have not been evaluated in MM cells. Therefore, in this study, we investigated the anticancer activity of GS in various MM cell lines (U266, MM.1S, and RPMI 8226) and the mechanisms involved. GS treatment of MM cells caused inhibition of cell proliferation and induction of apoptotic cell death as indicated by increased Bax protein expression, activation of caspases, and cleavage of poly (ADP-ribose) polymerase. This was associated with the downregulation of various proliferative and antiapoptotic gene products, including cyclin D, Bcl-2, Bcl-xL, and X-linked inhibitor of apoptosis protein. GS also suppressed the constitutive and interleukin 6-induced activation of STAT3. Interestingly, the inhibition of Janus activated kinase or STAT3 activity by the specific inhibitors or by siRNA knockdown of STAT3 resulted in the downregulation of HMGB1, suggesting an association between GS, STAT3, and HMGB1. Finally, GS potentiated the anticancer effects of bortezomib (BTZ) in MM cells. Herein, we demonstrated that GS could be a potential therapeutic agent for the treatment of MM, possibly alone or in combination with BTZ.

**Keywords:** guggulsterone; multiple myeloma; apoptosis; JAK/STAT signaling; anti-apoptotic proteins; HMGB1



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Original Article

# Detection of Antinuclear Antibodies Targeting Intracellular Signal Transduction, Metabolism, Apoptotic Processes and Cell Death in Critical COVID-19 Patients

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**Competing interests:** The authors declare no conflict of Interest.

**Abstract.** ***Background and Objectives*****: The heterogeneity of the coronavirus disease of 2019 (COVID-19) lies within its diverse symptoms and severity, ranging from mild to lethal. Acute respiratory distress syndrome (ARDS) is a leading cause of mortality in COVID-19 patients, characterized by a hyper cytokine storm. Autoimmunity is proposed to occur as a result of COVID-19, given the high similarity of the immune responses observed in COVID-19 and autoimmune diseases. Here, we investigate the level of autoimmune antibodies in COVID-19 patients with different severities. Results: Initial screening for antinuclear antibodies (ANA) IgG using ELISA revealed that 1.58% (2/126) and 4% (5/126) of intensive care unit (ICU) COVID-19 cases expressed strong and moderate ANA levels, respectively. An additional sample was positive with immunofluorescence assays (IFA) screening. However, all the non-ICU cases (n=273) were ANA negative using both assays. Samples positive for ANA were further confirmed with large-scale autoantibody screening by phage immunoprecipitation-sequencing (PhIP-Seq). The majority of the ANA-positive samples showed "speckled" ANA pattern by microscopy and revealed autoantibody specificities that targeted proteins involved in intracellular signal transduction, metabolism, apoptotic processes, and cell death by PhIP-Seq; further denoting reactivity to nuclear and cytoplasmic antigens. Conclusion: Our results further support the notion of routine screening for autoimmune responses in COVID-19 patients, which might help improve disease prognosis and patient management. Further, results provide compelling evidence that ANA-positive individuals should be excluded from being donors for convalescent plasma therapy in the context of COVID-19.**

**Keywords:** Autoimmunity; ANA; ICU; COVID-19; Coronavirus.

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pathogens

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*Review*

# Human Papillomaviruses-Related Cancers: An Update on the Presence and Prevention Strategies in the Middle East and North African Regions

**Queenie Fernandes [1,2,†], Soumaya Allouch [1,†], Ishita Gupta [3,*], Ibrahim Elmakaty [1], Khaled E. Elzawawi [1], Ahmed Amarah [1], Hamda Al-Thawadi [1], Halema Al-Farsi [1], Semir Vranic [1] and Ala-Eddin Al Moustafa [1,4,*]**

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**Abstract:** The human papillomavirus (HPV) is a non-enveloped double-stranded DNA virus capable of infecting skin and mucosa epithelial cells. Commonly, HPV infection is associated with sexually transmitted diseases and is considered the leading cause of cervical cancer and other carcinomas of the anogenital tract. However, several studies reported their involvement in cancers of non-sexual regions, including colorectal, head and neck, and breast cancers. There are several studies from the Middle East and North Africa (MENA) regions on the potential association between high-risk HPVs and cancer; nevertheless, there are limited studies that address the significance of HPV vaccination as a potential guard against these cancers. In the current review, we present a comprehensive description of the current HPV-associated cancers prevalence rates in the MENA region, demonstrating their steady increase with time, especially in African regions. Moreover, we discuss the potential impact of vaccination against HPV infections and its outcome on human health in this region.

**Keywords:** human papillomaviruses; cervical cancer; colorectal cancer; head and neck cancer; breast cancer; the Middle East and North African region

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## 1. Introduction

Cancer is one of the leading causes of mortality, with approximately 20 million new cancer cases worldwide and 10 million cancer deaths [1]. Along with environmental and genetic factors, recent studies attribute 20% of human cancers to viralor bacterial infections [2]; with several reports revealing the presence of viruses in both solid and non-solid tumors [3]. Some of the most commonly identified viruses include Epstein–Barr virus (EBV), human papillomaviruses (HPVs), human herpes virus 8 (HHV8 or Kaposi's sarcoma-associated herpesvirus), as well as hepatitis viruses B and C (HBV and HCV) [3]. Advancement in molecular biology showed viral oncogenes to alter cell signaling and growth control pathways, thus triggering the onset and development of human diseases, including cancer [4].

Human papillomaviruses (HPVs) are small, double-stranded DNA viruses with an icosahedral capsid belonging to the *Papillomaviridae* family and are the etiological agent of dermatological and sexually transmitted diseases [5]. Commonly, HPV is the most common cause of sexually transmitted infections worldwide, with once in a lifetime infection risk amongst both men and women of about 50% [6]. HPVs have the ability to infect the cutaneous and mucosal epithelial tissues of the skin, upper respiratory, and anogenital tracts [5]. Although HPVs are well-known inducers of common and anogenital warts [7],

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# The quality of energy- and macronutrient-balanced diets regulates host susceptibility to influenza in mice

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## SUMMARY

Modulation of individual macronutrients or caloric density is known to regulate host resistance to infection in mice. However, the impact of diet composition, independent of macronutrient and energy content, on infection susceptibility is unclear. We show that two laboratory rodent diets, widely used as standard animal feeds and experimental controls, display distinct abilities in supporting mice during influenza infection. Mice placed on the highly processed AIN93G showed increased mortality to infection compared with those on a grain-based chow diet, suggesting a detrimental role for highly processed food in host defense. We further demonstrate that the heightened susceptibility of AIN93G-fed mice was associated with the failure in homeostasis restoration mediated by the cytokine interferon (IFN)-γ. Our findings show that diet composition calibrates host survival threshold by regulating adaptive homeostasis and highlights a pivotal role for extrinsic signals in host phenotype and outcome of host-pathogen interaction.

## INTRODUCTION

Animal models for elucidating host defense mechanisms have traditionally focused on two interacting organisms: the pathogen and its host. However, it is now understood that environmental factors, such as diet, can also dictate host survival outcomes. While alterations of dietary macronutrients or caloric density are known to modulate infection susceptibility in mice,[1–5] the impact of the dietary composition, independent of macronutrient and energy content, on infection outcome is unknown. We have previously demonstrated that the interaction between macronutrients, rather than calorie intake, regulates physiology[6,7] and immune function[8] in health, highlighting the importance of studying the composition of energy-balanced diets in infection.

Laboratory animal diets can be divided into two categories: grain-based and those containing purified ingredients. Although both have equivalent protein, carbohydrate, and fat energy densities, grain-based and purified diets comprise of different ingredients, resulting in minor qualitative differences in the macro- and micronutrient content. For instance, grain-based diets typically obtain protein from soy instead of casein, thereby increasing the dietary phytoestrogen content.[9] Furthermore, grain-based diets include whole-food ingredients, whereas purified diets are equivalent to ultra-processed foods (UPFs) in human food systems.[10] There is growing evidence that UPFs are a major contributor to the global chronic disease burden,[11,12] in part, due to their palatability and nutritional composition (low in nutrient density, low in fiber, and energy dense).[13] There are also suggestions that the degree of processing per se is important.[14,15] Whether the same applies to resistance to infectious diseases is an important, but unanswered, question.

# Genomic architecture of autism from comprehensive whole-genome sequence annotation

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## Summary

Fully understanding autism spectrum disorder (ASD) genetics requires whole-genome sequencing (WGS). We present the latest release of the Autism Speaks MSSNG resource, which includes WGS data from 5,100 individuals with ASD and 6,212 non-ASD parents and siblings (total n= 11,312). Examining a wide variety of genetic variants in MSSNG and the Simons Simplex Collection (SSC; n= 9,205), we identified ASD-associated rare variants in 718/5,100 individuals with ASD from MSSNG (14.1%) and 350/2,419 from SSC (14.5%). Considering genomic architecture, 52% were nuclear sequence-level variants, 46% were nuclear structural variants (including copy-number variants, inversions, large insertions, uniparental isodisomies, and tandem repeat expansions), and 2% were mitochondrial variants. Our study provides a guidebook for exploring genotype-phenotype correlations in families who carry ASD-associated rare variants and serves as an entry point to the expanded studies required to dissect the etiology in the ~85% of the ASD population that remain idiopathic.

CORONAVIRUS



# High–temporal resolution profiling reveals distinct immune trajectories following the first and second doses of COVID-19 mRNA vaccines

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**Knowledge of the mechanisms underpinning the development of protective immunity conferred by mRNA vaccines is fragmentary. Here, we investigated responses to coronavirus disease 2019 (COVID-19) mRNA vaccination via high–temporal resolution blood transcriptome profiling. The first vaccine dose elicited modest interferon and adaptive immune responses, which peaked on days 2 and 5, respectively. The second vaccine dose, in contrast, elicited sharp day 1 interferon, inflammation, and erythroid cell responses, followed by a day 5 plasmablast response. Both post-first and post-second dose interferon signatures were associated with the subsequent development of antibody responses. Yet, we observed distinct interferon response patterns after each of the doses that may reflect quantitative or qualitative differences in interferon induction. Distinct interferon response phenotypes were also observed in patients with COVID-19 and were associated with severity and differences in duration of intensive care. Together, this study also highlights the benefits of adopting high-frequency sampling protocols in profiling vaccine-elicited immune responses.**

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) vaccines are critical to the ongoing efforts to control the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. To date, 9 vaccines have received some form of approval for use in humans, and phase 3 trials are ongoing for an additional 11 vaccines (*1*). Notable differences exist among the vaccine products in terms of their design, the levels of protection they confer, and the type, incidence, and severity of adverse events they may elicit. Gaining a comprehensive understanding of the immunological factors underpinning the different responses to various vaccines is a major endeavor. Yet, this knowledge is necessary for guiding timely decisions to modulate vaccination protocols (e.g., the use of different types of vaccines for the first and second vaccine doses). This information may also assist in matching individuals with the growing number of available vaccines based on their demographics, health status, or any other relevant clinical/molecular phenotypes.

Blood transcriptome profiling measures the abundance of transcripts in whole blood on a system-wide scale. It was previously used to comprehensively profile the immune responses elicited by

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Journal of Translational Medicine

RESEARCH Open Access

# Assessing the genetic burden of familial hypercholesterolemia in a large middle eastern biobank

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## Abstract

**Background** The genetic architecture underlying Familial Hypercholesterolemia (FH) in Middle Eastern Arabs is yet to be fully described, and approaches to assess this from population-wide biobanks are important for public health planning and personalized medicine.

**Methods** We evaluate the pilot phase cohort (n = 6,140 adults) of the Qatar Biobank (QBB) for FH using the Dutch Lipid Clinic Network (DLCN) criteria, followed by an in-depth characterization of all genetic alleles in known dominant (*LDLR*, *APOB*, and *PCSK9*) and recessive (*LDLRAP1*, *ABCG5*, *ABCG8*, and *LIPA*) FH-causing genes derived from whole-genome sequencing (WGS). We also investigate the utility of a globally established 12-SNP polygenic risk score to predict FH individuals in this cohort with Arab ancestry.

**Results** Using DLCN criteria, we identify eight (0.1%) 'definite', 41 (0.7%) 'probable' and 334 (5.4%) 'possible' FH individuals, estimating a prevalence of 'definite or probable' FH in the Qatari cohort of ~ 1:125. We identify ten previously known pathogenic single-nucleotide variants (SNVs) and 14 putatively novel SNVs, as well as one novel copy number variant in *PCSK9*. Further, despite the modest sample size, we identify one homozygote for a known pathogenic variant (*ABCG8*, p. Gly574Arg, global MAF = 4.49E-05) associated with Sitosterolemia 2. Finally, calculation of polygenic risk scores found that individuals with 'definite or probable' FH have a significantly higher LDL-C SNP score than 'unlikely' individuals (p = 0.0003), demonstrating its utility in Arab populations.

**Conclusion** We design and implement a standardized approach to phenotyping a population biobank for FH risk followed by systematically identifying known variants and assessing putative novel variants contributing to FH burden in Qatar. Our results motivate similar studies in population-level biobanks – especially those with globally under-represented ancestries – and highlight the importance of genetic screening programs for early detection and management of individuals with high FH risk in health systems.

**Keywords** Cholesterol, Dyslipidemias, LDL, Lipoproteins/Receptors, Premature coronary artery disease, Dutch lipid Clinic Network, *LDLRAP1*, Sitosterolemia, Polygenic risk scores, Middle East region.

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Review article

# Functional roles of lncRNA-TUG1 in hepatocellular carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) or hepatoma is malignant cancer that starts from the main liver cells. Although various classical methods have been used for patients with HCC, various molecular mechanisms involved in HCC progression should be invested. Previous studies demonstrated that abnormal expression of long non-coding RNAs (lncRNAs) presented important roles in the pathogenesis of HCC cells. LncRNA TUG1 was found to mediate HCC cell growth, EMT, and metastasis. Therefore, targeting TUG1 and its downstream genes may be a suitable approach for patients with HCC. In this review, we summarized the potential roles of TUG1 in HCC.

## 1. Introduction

Liver cancer is still a global health issue and its prevalence is increasing worldwide [1]. This cancer is the sixth most common cancer in both males and females, and also the third leading cause of cancer-related death [2]. Hepatocellular carcinoma (HCC) is a heterogeneous malignancy that can be caused by chronic hepatitis B virus (HBV) [3] or hepatitis C virus (HCV) infection [4], metabolic diseases [5], chronic alcohol consumption [6], autoimmune hepatitis [7], type 2 diabetes mellitus (T2DM) [8] and obesity [9]. Diagnosis of HCC requires advanced medical imaging techniques such as computed tomography (CT scan) or magnetic resonance imaging (MRI), in combination with an alpha-fetoprotein tumor marker test without the need for histologic confirmation [11,12]. However, due to the high rate of false positives, confirmation by tissue biopsy are used in some cases [13]. Despite significant progress in cancer diagnosis, HCC is still a late-stage disease and only 44 % of patients are diagnosed with localized disease [14]. Patients with early and intermediate-stage HCC may benefit from surgical resection, local radiofrequency ablation, systemic targeted drugs, and transarterial chemoembolization [15,16]. However, the efficacy of these treatments is limited by a lack of understanding and the non-uniformity of HCC symptoms [17]. Another significant challenge to treating HCC patients is high incidence of recurrence and metastasis after treatment [18]. Thus, deciphering the precise mechanisms behind HCC and developing new biomarkers for surveillance and early identification may improve patient survival [19,20]. HCC can be developed as a result of multi-step biological processes, genetic alterations, oxidative stress, cellular microenvironment, and inflammation [21,22]. Recent studies have shown that genetic alterations alone cannot fully explain the heterogeneity of cancer and epigenetic modification is another driver of human cancers [23,24]. Several epigenetic regulators including DNA methylation, histone changes, and non-coding RNAs (ncRNAs) are fundamental to the development and progression of cancer [25]. ncRNAs play critical roles in several physiological and pathological processes [26,27]. ncRNAs can be classified and separated into different categories based on their size and function [28]. There are two main types of ncRNAs, structural ncRNAs and regulatory ncRNAs [29]. Regulatory ncRNAs can be generically classified into short (< 30 nts),

*Abbreviations:* ceRNA, competitive endogenous RNA; lncRNAs, long non-coding RNAs; TUG1, Taurine Up-regulated Gen; PRC2, polycomb repressive complex 2; ZEB1, Zinc finger E-box-binding homeobox 1.

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REVIEW Open Access

# Integration of CRISPR/Cas9 with artificial intelligence for improved cancer therapeutics

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## Abstract

Gene editing has great potential in treating diseases caused by well-characterized molecular alterations. The introduction of clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9)–based gene-editing tools has substantially improved the precision and efficiency of gene editing. The CRISPR/Cas9 system offers several advantages over the existing gene-editing approaches, such as its ability to target practically any genomic sequence, enabling the rapid development and deployment of novel CRISPR-mediated knock-out/knock-in methods. CRISPR/Cas9 has been widely used to develop cancer models, validate essential genes as druggable targets, study drug-resistance mechanisms, explore gene non-coding areas, and develop biomarkers. CRISPR gene editing can create more-effective chimeric antigen receptor (CAR)-T cells that are durable, cost-effective, and more readily available. However, further research is needed to define the CRISPR/Cas9 system's pros and cons, establish best practices, and determine social and ethical implications. This review summarizes recent CRISPR/Cas9 developments, particularly in cancer research and immunotherapy, and the potential of CRISPR/Cas9-based screening in developing cancer precision medicine and engineering models for targeted cancer therapy, highlighting the existing challenges and future directions. Lastly, we highlight the role of artificial intelligence in refining the CRISPR system's on-target and off-target effects, a critical factor for the broader application in cancer therapeutics.

**Keywords:** CRISPR/Cas9, Artificial intelligence, Genome engineering, Cancer precision medicine, Cancer Immunotherapy, CAR T-cells, Epigenetics, Drug resistance, Cancer biomarker

## Introduction

As our understanding of the underlying genetic and molecular basis of malignancy has rapidly increased through massive tumor genetic profiling, modeling, and characterization, the ever-evolving list of molecular alterations in cells holds great potential for identifying actionable genomic events and treating malignancies. The emergence of gene-editing tools in the last few decades has enabled scientists to manipulate genomic sequences to understand gene function better and develop targeted treatments for inherited and acquired diseases. Although the 1970 discovery of restriction enzymes, the original genome editor, was a breakthrough enabling the

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REGULAR ARTICLE

blood advances

# CD14$^+$/CD31$^+$ monocytes expanded by UM171 correct hemophilia A in zebrafish upon lentiviral gene transfer of factor VIII

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**Key Points**

- A flow cytometry–based blood screening revealed that HSC transmit native and lentiviral vector transgenic FVIII preferentially to CD14$^+$/CD31$^+$ monocytes.
- CD14$^+$/CD31$^+$ monocytes derived from FVIII-transduced HSC rescued the bleeding phenotype in a novel zebrafish model of hemophilia A.

Emerging gene therapy clinical trials test the correction of hemophilia A (HA) by replacing factor VIII (FVIII) in autologous hematopoietic stem cells (HSCs). Although it is known that platelets, monocyte/macrophages, and mesenchymal stromal cells can secrete transgenic FVIII, a systematic examination of blood lineages as extrahepatic sources of FVIII, to our knowledge, has not yet been performed. In this study, we sought to provide a comprehensive map of native and lentivirus-based transgenic FVIII production from HSC stage to mature blood cells, through a flow cytometry analysis. In addition, we generated a model of transient HA in zebrafish based on antisense RNA, to assess the corrective potential of the FVIII-transduced HSCs. We discovered that FVIII production begins at the CD34$^+$ progenitor stage after cytokine stimulation in culture. Among all mature white blood cells, monocytes are the largest producers of native FVIII and can maintain protein overexpression during differentiation from HSCs when transduced by a FVIII lentiviral vector. Moreover, the addition of the HSC self-renewal agonist UM171 to CD34$^+$ cells during transduction expanded a subpopulation of CD14$^+$/CD31$^+$ monocytes with excellent ability to carry the FVIII transgene, allowing the correction of HA phenotype in zebrafish. Finally, the HA zebrafish model showed that *f8* RNA is predominantly localized in the hematopoietic system at the larval stage, which indicates a potential contributory role of FVIII in hematopoiesis that warrants further investigation. We believe that this study may be of broad interest to hematologists and researchers striving to advance knowledge and permanent treatments for patients with HA.

## Introduction

Hemophilia A (HA) is an X-linked monogenic bleeding disorder caused by dysfunction or deficiency of factor VIII (FVIII); HA affects ~800 000 individuals worldwide (World Federation of Hemophilia Annual Global Survey 2020 https://www1.wfh.org/publications/files/pdf-2045.pdf). The use of viral vectors

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Data are available on request from the corresponding author, Sara Deola (sdeola@sidra.org).

The full-text version of this article contains a data supplement.

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ORIGINAL ARTICLE

# Characterization of bacterial diversity and capacity to remove lead of a consortium from mining soil

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## Abstract

**Introduction** At present, the presence of lead ($Pb^{2+}$) continues to be a problem in water bodies due to its continuous use and high toxicity. The aim of this study was to investigate the bacterial diversity of a potential consortium used as a biosorbent for the removal of lead in an aqueous solution.

**Methods** The minimum inhibitory concentration and the mean lethal dose of the consortium were determined, and then the optimal variables of pH and temperature for the removal process were obtained. With the optimal conditions, the kinetic behavior was evaluated, and adjustments were made to different mathematical models. A Fourier transform infrared spectroscopy analysis was performed to determine the functional groups of the biomass participating in the removal process, and the diversity of the bacterial consortium was evaluated during $Pb^{2+}$ removal by an Ion Torrent Personal Genome Machine System.

**Results** It was found that the intraparticle diffusion model was the one that described the adsorption kinetics showing a higher rate constant with a higher concentration of $Pb^{2+}$, while the Langmuir model was that explained the isotherm at 35 °C, defining a maximum adsorption load for the consortium of 54 mg/g. In addition, it was found that $Pb^{2+}$ modified the diversity and abundance of the bacterial consortium, detecting genera such as *Pseudomonas*, *Enterobacter, Citrobacter*, among others.

**Conclusions** Thus, it can be concluded that the bacterial consortium from mining soil was a biosorbent with the ability to tolerate high concentrations of $Pb^{2+}$ exposure. The population dynamics during adsorption showed enrichment of Proteobacteria phyla, with a wide range of bacterial families and genera capable of resisting and removing $Pb^{2+}$ in solution.

**Keywords** Consortium · Lead · Bioadsorption · Biodiversity · Minimum inhibitory concentration

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## Introduction

Lead ($Pb^{2+}$) is one of the most studied toxic metals, and its adverse health effects have been firmly established for decades. The World Health Organization considers it one of the 10 chemical elements of greatest concern for public health, causing 600,000 new cases of intellectual disability in the world every year (World Health Organization, 2016; Naranjo et al. 2020). Unfortunately, as mentioned by Frank et al. (2019), lead inputs derived from paint and gasoline persist in the environment, while economic and technological incentives prioritize the continuous use and emission of lead, making it part of our daily life in the form of electronic products, batteries, paints and dyes, enamels, cosmetic makeup, and ammunition. In addition to anthropogenic sources of lead, site-specific geology contributes to the contamination of soil, aquifers, air, dust, and even food (Pieper et al. 2015). These activities induce adverse effects on human and animal

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Protocol

# Analytic pipelines to assess the relationship between immune response and germline genetics in human tumors

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## SUMMARY

**Germline genetic variants modulate human immune response. We present analytical pipelines for assessing the contribution of hosts' genetic background to the immune landscape of solid tumors using harmonized data from more than 9,000 patients in The Cancer Genome Atlas (TCGA). These include protocols for heritability, genome-wide association studies (GWAS), colocalization, and rare variant analyses. These workflows are developed around the structure of TCGA but can be adapted to explore other repositories or in the context of cancer immunotherapy.**

**For complete details on the use and execution of this protocol, please refer to Sayaman et al. (2021).**

## BEFORE YOU BEGIN

These protocols describe specific bioinformatic workflows for the analyses of The Cancer Genome Atlas (TCGA) genomic datasets and well-characterized immune traits (Thorsson et al., 2018). However, these methodologies can also be applied to other datasets with similar structures. The majority

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MDPI

*Article*

# The Genetic Spectrum of Maturity-Onset Diabetes of the Young (MODY) in Qatar, a Population-Based Study

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**Abstract:** Maturity-onset diabetes of the young (MODY) is a rare monogenic form of diabetes mellitus. In this study, we estimated the prevalence and genetic spectrum of MODY in the Middle Eastern population of Qatar using whole-genome sequencing (WGS) of 14,364 subjects from the population-based Qatar biobank (QBB) cohort. We focused our investigations on 14 previously identified genes ascribed to the cause of MODY and two potentially novel MODY-causing genes, *RFX6* and *NKX6-1*. Genetic variations within the 16 MODY-related genes were assessed for their pathogenicity to identify disease-causing mutations. Analysis of QBB phenotype data revealed 72 subjects (0.5%) with type 1 diabetes, 2915 subjects (20.3%) with type 2 diabetes and 11,377 (79.2%) without diabetes. We identified 22 mutations in 67 subjects that were previously reported in the Human Genetic Mutation Database (HGMD) as disease-causing (DM) or likely disease causing (DM?) for MODY. We also identified 28 potentially novel MODY-causing mutations, predicted to be among the top 1% most deleterious mutations in the human genome, which showed complete (100%) disease penetrance in 34 subjects. Overall, we estimated that MODY accounts for around 2.2–3.4% of diabetes patients in Qatar. This is the first population-based study to determine the genetic spectrum and estimate the prevalence of MODY in the Middle East. Further research to characterize the newly identified mutations is warranted.

**Keywords:** maturity-onset diabetes of the young; MODY; diabetes; *HNF1A*; *HNF4A*; *GCK*



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## 1. Introduction

Maturity-onset diabetes of the young (MODY) is a rare monogenic form of diabetes mellitus, accounting for approximately 1–5% of diabetes cases worldwide [1]. MODY is an autosomal dominant condition, clinically characterized by a multigenerational family history of diabetes and absence of pancreatic β-cell autoantibodies, and disease onset before the age of 25 years in most cases. A prominent feature of MODY includes progressive β-cell dysfunction, while in some cases it could be associated with other organ abnormalities, such as kidney abnormalities and fat malabsorption [2]. Patients with MODY are often misdiagnosed due to similarities in their clinical manifestations to those with other forms of diabetes [3]. To date, 14 genes are ascribed to the cause of MODY, each encoding for a different subtype [2]. Recent studies have identified novel variants in two genes encoding regulatory factor X6 (*RFX6*) and NK6 Homeobox 1 (*NKX6-1*) as possible MODY contributors [4,5].

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Review article

# The role of dietary antioxidants in type 2 diabetes and neurodegenerative disorders: An assessment of the benefit profile

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ABSTRACT

Healthy diet is vital to cellular health. The human body succumbs to numerous diseases which afflict severe economic and psychological burdens on the patient and family. Oxidative stress is a possible crucial regulator of various pathologies, including type 2 diabetes and neurodegenerative diseases. It generates reactive oxygen species (ROS) that trigger the dysregulation of essential cellular functions, ultimately affecting cellular health and homeostasis. However, lower levels of ROS can be advantageous and are implicated in a variety of signaling pathways. Due to this dichotomy, the terms oxidative "eustress," which refers to a good oxidative event, and "distress," which can be hazardous, have developed. ROS affects multiple signaling pathways, leading to compromised insulin secretion, insulin resistance, and β-cell dysfunction in diabetes. ROS is also associated with increased mitochondrial dysfunction and neuroinflammation, aggravating neurodegenerative conditions in the body, particularly with age. Treatment includes drugs/therapies often associated with dependence, side effects including non-selectivity, and possible toxicity, particularly in the long run. It is imperative to explore alternative medicines as an adjunct therapy, utilizing natural remedies/resources to avoid all the possible harms. Antioxidants are vital components of our body that fight disease by reducing oxidative stress or nullifying the excess toxic free radicals produced under various pathological conditions. In this review, we focus on the antioxidant effects of components of dietary foods such as tea, coffee, wine, oils, and honey and the role and mechanism of action of these antioxidants in alleviating type 2 diabetes and neurodegenerative disorders. We aim to provide information about possible alternatives to drug treatments used alone or combined to reduce drug intake and encourage the consumption of natural ingredients at doses adequate to promote health and combat pathologies while reducing unwanted risks and side effects.

## 1. Introduction

Cellular oxidative stress (OS), which occurs due to a reduction-oxidation (redox) imbalance in the cell, produces reactive free radicals that can damage cells and tissues. Free radicals can have several centers, such as oxygen, nitrogen, sulfur and carbon. These

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SHORT COMMUNICATION

# Successful transitioning children and adolescents with type 1 diabetes from multiple daily injections to advanced hybrid closed-loop system in 10 days: a prospective intervention study on MiniMed 780G system

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**Keywords** Type 1 diabetes · Continuous subcutaneous insulin infusion · Continuous glucose monitoring · Diabetes education · Closed-loop systems

## Introduction

One of the latest automated insulin Delivery (AID) systems is the advanced hybrid closed-loop (AHCL), the MiniMed 780G system (Medtronic, Northridge, CA, USA), which automatically delivers basal insulin with a customizable glucose target in addition to automated bolus correction, as required. Several studies [1–3] have shown that AID systems in people with type 1 diabetes (T1D) previously treated with insulin pump therapy can improve HbA1c and reduce time in hyperglycemia without increasing hypoglycemia. To the best of our knowledge, this is the first clinical experience on AHCL MiniMed 780G system in people with T1D, previously treated with multiple daily injections (MDI), without prior pump experience.

The objective of this study was to evaluate the glycemic outcome using AHCL Minimed 780G system in children and adolescents with T1D on MDI therapy.

## Methods

In this perspective, single-center, single-arm, intervention study on AHCL MiniMed 780G system with Guardian 3 sensor (Medtronic, Northridge, CA USA), we recruited children and adolescents (aged 7–17 years) attending diabetes clinics at Sidra Medicine (Doha, Qatar) on a first-come, first-served basis with the following inclusion criteria (T1D, HbA1c < 12.5%, MDI for at least one year, with or without continuous glucose monitoring (CGM), no prior pump experience) and exclusion criteria (Total Daily Dose (TDD) < 8 units and no diabetes ketoacidosis (DKA) in the last 6 months). Individuals' responsibilities (carbohydrate counting, bolusing before meal, calibrating the system 3–4 times per day, responding to alerts and alarms, downloading pump data from home) were discussed prior pump training. All individuals recruited in the study were able to count carbohydrates, which was evaluated by a registered dietitian.

The study (IRB00009930) was approved by the local and National Ethics Committee in Qatar, and all participants and their guardians signed a written informed assent/consent before the start of study-related procedures. This study (ClinicalTrials.gov NCT03755479) was funded by Sidra Medicine, Doha.

AHCL system training was performed as a group session (2–4 individuals, four sessions of two hours on four consecutive days. CGM was initiated on the first day of the training, for education and observational purposes. Participants initiated the AHCL system in ten days: four days of training with additional three days of practicing (no insulin delivery by pump) to gain more experience and confidence with the sensor, followed by 3 days (72 h) of manual mode to allow the algorithm to collect insulin utilization and CGM data to establish personalized parameters for AHCL initiation [4]. The initial pump settings were calculated as follows: 10–20% reduction of total daily dose, with a 40/60 basal/bolus distribution in four or five basal rates. Insulin to carbohydrate ratio (ICR) settings utilizes the formula of 300–450/total

Managed by Antonio Secchi .

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ORIGINAL ARTICLE

# Genotyping and Drug Resistance Profile of Clinical Isolates of *Candida albicans* from Vulvovaginal Candidiasis in the Eastern China

**Nan Hong · Yan Lei · Huan Chen · Xiaofei Chen · Kin Ming Tsui · Danyang Hu · Wanqing Liao · Liang Yan · Hong Zhang · Rongfen Zhao · Gang Wu · Nong Yu · Shuwen Deng**

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**Abstract** A total of 244 *Candida albicans* isolates recovered from vulvovaginal candidiasis (VVC) patients in Suzhou, Eastern China, were investigated. According to CLSI documents M27-A4 and M59-3ed/M60-2ed, the MIC geometric means of nine antifungals in increasing order were micafungin (0.048 mg/L), anidulafungin (0.132 mg/L), caspofungin (0.19 mg/L), itraconazole (0.23 mg/L), posaconazole (0.25 mg/L), voriconazole (0.28 mg/L), 5-flucytosine (0.44 mg/L), amphotericin B (0.49 mg/L) and fluconazole (2.01 mg/L) respectively. Of note, 6.5% (16/244) *C. albicans* isolates showed resistance mainly to anidulafungin (mono-echinocandin resistance), while voriconazole had the lowest susceptibility rate of 34.8% (85/244), followed by fluconazole 59.4% (145/244), respectively. All isolates were genotyped by allelic combination of 3 microsatellite markers (CEF3, CAIII and LOC4). A total of 129 different allelic genotypes were identified, in which seven different clades were recognized with a discriminatory power of 0.96. Genotypes A-D were present in 35% of the isolates. In conclusion, decrease in antifungal drug susceptibility to *C. albicans* isolates from VVC is alarming. Our findings revealed the genetic diversity of *C. albicans* isolates among VVC

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# Multisystem inflammatory syndrome in children (MIS-C) related to COVID-19 infection in the state of Qatar: Association with Kawasaki-like Illness

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**Abstract.** *Introduction:* World Health Organization (WHO) is encouraging reporting of children with Multisystem Inflammatory Syndrome (MIS-C) associated with SARS-CoV-2 infection for better understanding and management of the disease. *Methodology*: This retrospective study included the first 15 pediatrics patient with a confirmed diagnosis of MIS-C associated with SARS-CoV-2 infection in the state of Qatar. We studied and analyzed their demographic data, clinical manifestations, laboratory tests, treatment, and outcome. *Results:* A total of 15 children were studied (mean age 3.5 ± 2.7 year). Recent severe acute respiratory syndrome coronavirus 2 infection was identified in all of them (100%). The majority of these patients had 4 or more systems involvement. Nine of the 15 presented with Kawasaki disease - picture and all had gastrointestinal symptoms (vomiting and diarrhea). Five required Pediatrics Intensive Care Unit (PICU) admission. Lab investigations revealed high D-Dimer, hyponatremia, and hypoalbuminemia in all. Low hemoglobin (Hb), thrombocytopenia, and sterile pyuria occurred in 86.6%, 60% and 75% of them, respectively. Treatment with combined anti-inflammatory medications (intravenous immunoglobulin, corticosteroids) was used in along with immunomodulatory agents (Anakinra) in a selected group of refractory patients. No mortality happened. *Conclusion:* Our young children who presented with MIS-C related to SARS-CoV-2 infection had significantly higher Kawasaki-disease picture compared to other reports. One third of them required PICU admission but no mortality occurred. (www.actabiomedica.it)

**Key word:** SARS-CoV-2 infection, Multisystem Inflammatory Syndrome (MIS-C), infants, children, treatment, Qatar.

## Introduction

Qatar is one of over 200 countries reported to be affected by the COVID-19 pandemic, with a current prevalence of the disease affecting more than 100,000 inhabitants (1). Children and adolescents are reported to experience fewer symptoms of the acute virus infection compared to adults. However, there are increasing number of reports of SARS-CoV-2 infection-related complications, including multisystem inflammatory syndrome in children (MIS-C).

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Original article

# Growth, bone maturation and ovarian size in girls with early and fast puberty (EFP) and effects of three years treatment with GnRH analogue (GnRHa)

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**Abstract.** *Introduction:* Early puberty (EP) in girls is defined as the onset of thelarche that begins after 6 years and before 8 years and/or acceleration in the tempo of pubertal development. The stage of puberty and the ovarian volume at presentation and the effect of treatment with GnRH analogue (GnRHa) on final adult height are still debated. *Patients and methods:* We analyzed the data of 22 girls, who presented early and fast puberty (FEP). The clinical stage of puberty, hormonal levels, and ovarian volume (OV) (measured by ovarian ultra-sonography) at presentation were studied. We recorded the effects of 3 years of treatment with GnRHa on their growth in relation to their mid parental height, pubertal progression, and bone maturation. *Results:* At presentation, the mean age of girls was 7.7 ± 0.7 yr , Ht-SDS was 0.8 ± 0.9, and growth velocity (GV) was 8.7 ± 1.4 cm. Bone age was advanced by 1.9 ± 1 yr compared to their chronological age. The difference between their standing height (Z-Score: Ht-SDS) and their mid-parental Ht-SDS (MPht-SDS) was 1.4 ± 0.7. Their predicted final adult height (FA-Ht) was 155 ± 8cm. After 3 years of using GnRHa (Triptorelin:3.75 mg I.M. monthly), their mean Ht-SDS was 0.5 ± 1.5, associated with reduced growth velocity (GV: 5 ± 1.5 cm/yr) and deceleration of bone age (0.7± 0.8 yr compared to their chronological age). The difference between their Ht-SDS and their MPht-SDS was 1.2 ± 1 and their predicted FA-Ht improved to 159 ± 9cm. Their average MPht was 159 ± 4 cm. There was no change in breast development during the 3 years of therapy. The BMI-SDS significantly increased from 1.3 ± 0.7 before treatment to 1.7 ± 0.8 after 3 years of treatment ($P = 0.001$). At presentation, the mean OV was 2.3 ± 1.2mL. The OV correlated significantly with breast and pubic hair Tanner stages ($r = 0.34$, and 0.56, respectively; $P: < 0.05$). There was also a significant correlation between OV and the hormonal profile (LH, FSH, 17β-estradiol and IGF-1 levels; $r = 0.80$, 0.54, 0.485 and 0.40, respectively; $P: < 0.05$). There was no correlation between OV and bone age. Larger OV at presentation was associated with reduced Ht-SDS after 3 years of GnRHa treatment ($r = 0.42$, $P: < 0.01$) and negatively with the difference between Ht-SDS and MPH-SDS at the end of treatment (lower potential for growth; $r = 0.47$, $P: < 0.01$). *Conclusion:* GnRHa therapy decreased the fast progress of puberty, skeletal maturation, and GV/year. It was successful in increasing the predicted final adult height comparable to or surpassing their mid-parenteral height. A larger OV at presentation was associated with reduced Ht-SDS after 3 years of GnRHa treatment. Clearly, a definitive evaluation of the efficacy of GnRHa as a treatment for EFP in girls will require expanded and concerted studies. (www.actabiomedica.it)

**Key words:** Early and fast puberty (FEP), growth, bone maturation, ovarian size, GnRH analogue treatment

BMJ Open

# Biomarker-guided duration of Antibiotic Treatment in Children Hospitalised with confirmed or suspected bacterial infection (BATCH): protocol for a randomised controlled trial

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## ABSTRACT

**Introduction** Procalcitonin (PCT) is a biomarker more specific for bacterial infection and responds quicker than other commonly used biomarkers such as C reactive protein, but is not routinely used in the National Health Service (NHS). Studies mainly in adults show that using PCT to guide clinicians may reduce antibiotic use, reduce hospital stay, with no associated adverse effects such as increased rates of hospital re-admission, incomplete treatment of infections, relapse or death. A review conducted for National Institute for Health and Care Excellence recommends further research on PCT testing to guide antibiotic use in children.

**Methods and analysis** Biomarker-guided duration of Antibiotic Treatment in Children Hospitalised with confirmed or suspected bacterial infection is a multicentre, prospective, two-arm, individually Randomised Controlled Trial (RCT) with a 28-day follow-up and internal pilot. The intervention is a PCT-guided algorithm used in conjunction with best practice. The control arm is best practice alone. We plan to recruit 1942 children, aged between 72 hours and up to 18 years old, who are admitted to the hospital and being treated with intravenous antibiotics for suspected or confirmed bacterial infection. Coprimary outcomes are duration of antibiotic use and a composite safety measure. Secondary outcomes include time to switch from broad to narrow spectrum antibiotics, time to discharge, adverse drug reactions, health utility and cost-effectiveness. We will also perform a qualitative process evaluation. Recruitment commenced in June 2018 and paused briefly between March and May 2020 due to the COVID-19 pandemic.

**Ethics and dissemination** The trial protocol was approved by the HRA and NHS REC (North West Liverpool East REC reference 18/NW/0100). We will publish the results in international peer-reviewed journals and present at scientific meetings.

**Trial registration number** ISRCTN11369832.

## Strengths and limitations of this study

- ► Trial will evaluate both safety and effectiveness of procalcitonin to guide antibiotic duration in children hospitalised with suspected or confirmed bacterial infection.
- ► Randomised controlled trial with multicentre design including patients from hospital sites in England and Wales.Efficient trial design with coprimary endpoints and including a health economic analysis and qualitative process evaluation.
- ► Due to the type of intervention it is not possible to blind patients and clinicians.
- ► Potential shift in patient population following a recruitment break due to COVID-19 pandemic will be addressed with sensitivity analyses.

## INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] Sepsis causes many non-specific symptoms and signs that can also be caused by a large number of conditions that may or may not be due to infection, and that may or may not require immediate or urgent treatment. Sepsis is usually caused by bacteria, although viral and fungal causes do occur. The problem for clinicians is the difficulty in distinguishing bacterial sepsis from other conditions presenting with similar non-specific signs and symptoms. Prompt administration of antibiotics reduces mortality by half,[2] but indiscriminate antibiotic use unnecessarily increases antimicrobial resistance (AMR), resulting in increased

nature COMMUNICATIONS

ARTICLE

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# Relative infectiousness of SARS-CoV-2 vaccine breakthrough infections, reinfections, and primary infections

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SARS-CoV-2 breakthrough infections in vaccinated individuals and in those who had a prior infection have been observed globally, but the transmission potential of these infections is unknown. The RT-qPCR cycle threshold (Ct) value is inversely correlated with viral load and culturable virus. Here, we investigate differences in RT-qPCR Ct values across Qatar's national cohorts of primary infections, reinfections, BNT162b2 (Pfizer-BioNTech) breakthrough infections, and mRNA-1273 (Moderna) breakthrough infections. Our matched-cohort analyses of the randomly diagnosed infections show higher mean Ct value in all cohorts of breakthrough infections compared to the cohort of primary infections in unvaccinated individuals. The Ct value is 1.3 (95% CI: 0.9–1.8) cycles higher for BNT162b2 breakthrough infections, 3.2 (95% CI: 1.9–4.5) cycles higher for mRNA-1273 breakthrough infections, and 4.0 (95% CI: 3.5–4.5) cycles higher for reinfections in unvaccinated individuals. Since Ct value correlates inversely with SARS-CoV-2 infectiousness, these differences imply that vaccine breakthrough infections and reinfections are less infectious than primary infections in unvaccinated individuals. Public health benefits of vaccination may have been underestimated, as COVID-19 vaccines not only protect against acquisition of infection, but also appear to protect against transmission of infection.

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ORIGINAL RESEARCH

# Effect of nutrition status and inflammatory stimuli on ghrelin and peptide-YY levels among critically ill children: A prospective and observational study

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**Funding information**
The Evelyn Trust

## Abstract

**Background:** Ghrelin and peptide-YY (PYY) are two gut peptides with apparent opposing actions. In normal conditions, ghrelin and PYY work together in synergy to regulate energy homeostasis. During critical illness, series of metabolic, endocrine, and inflammatory changes take place in response to a severe insult. Emerging studies recorded alterations in gut hormone levels in critically ill adults. This study aims to assess the effect of inflammation, nutrition, and feeding status on ghrelin and PYY levels in critically ill children.

**Methods:** In this prospective study, we collected blood samples from critically ill children on days 2 or 3 of pediatric intensive care unit (PICU) admission for the analysis of serum ghrelin, PYY, and inflammatory markers. Data related to the intake anthropometry, as well as other clinical data, were collected from patients' records. Multiple linear regression analysis was used to identify factors affecting serum levels of these hormones.

**Results:** Forty-two children admitted to the PICU were included in this study. Ghrelin level was influenced by admission nutrition status of the children and age. PYY was influenced by macronutrient intake and age. Inflammatory markers also showed an association with the measured levels of these hormones, with C-reactive protein being positively associated with ghrelin levels and tumor necrosis factor alpha showing a positive association with PYY levels.

**Conclusion:** Although ghrelin and PYY have been linked to feeding status in healthy patients, during critical illness there might be other factors, such as inflammation and nutrition status, that might contribute to the changes observed in ghrelin/PYY profiles.

KEYWORDS
enteral nutrition, ghrelin, inflammation, pediatrics, PYY

PLOS ONE

RESEARCH ARTICLE

# Assessing the performance of a serological point-of-care test in measuring detectable antibodies against SARS-CoV-2

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## Abstract

This study investigated the performance of a rapid point-of-care antibody test, the BioMedomics COVID-19 IgM/IgG Rapid Test, in comparison with a high-quality, validated, laboratory-based platform, the Roche Elecsys Anti-SARS-CoV-2 assay. Serological testing was conducted on 709 individuals. Concordance metrics were estimated. Logistic regression was used to assess associations with seropositivity. SARS-CoV-2 seroprevalence was 63.5% (450/709; 95% CI 59.8%-67.0%) using the BioMedomics assay and 71.9% (510/709; 95% CI 68.5%-75.2%) using the Elecsys assay. There were 60 discordant results between the two assays, all of which were seropositive in the Elecsys assay, but seronegative in the BioMedomics assay. Overall, positive, and negative percent agreements between the two assays were 91.5% (95% CI 89.2%-93.5%), 88.2% (95% CI 85.1%-90.9%), and 100% (95% CI 98.2%-100%), respectively, with a Cohen's kappa of 0.81 (95% CI 0.78–0.84). Excluding specimens with lower (Elecsys) antibody titers, the agreement improved with overall, positive, and negative percent concordance of 94.4% (95% CI 92.3%-96.1%), 91.8% (95% CI 88.8%-94.3%), and 100% (95% CI 98.2%-100%), respectively, and a Cohen's kappa of 0.88 (95% CI 0.85–0.90). Logistic regression confirmed better agreement with higher antibody titers. The BioMedomics COVID-19 IgM/IgG Rapid Test demonstrated good performance in measuring detectable antibodies against SARS-CoV-2, supporting the

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Healthcare Informatics Research

# Impact of Universal Suicide Risk Screening in a Pediatric Emergency Department: A Discrete Event Simulation Approach

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**Objectives:** The aim of this study was to use discrete event simulation (DES) to model the impact of two universal suicide risk screening scenarios (emergency department [ED] and hospital-wide) on mean length of stay (LOS), wait times, and overflow of our secure patient care unit for patients being evaluated for a behavioral health complaint (BHC) in the ED of a large, academic children's hospital. **Methods:** We developed a conceptual model of BHC patient flow through the ED, incorporating anticipated system changes with both universal suicide risk screening scenarios. Retrospective site-specific patient tracking data from 2017 were used to generate model parameters and validate model output metrics with a random 50/50 split for derivation and validation data. **Results:** The model predicted small increases (less than 1 hour) in LOS and wait times for our BHC patients in both universal screening scenarios. However, the days per year in which the ED experienced secure unit overflow increased (existing system: 52.9 days; 95% CI, 51.5–54.3 days; ED: 94.4 days; 95% CI, 92.6–96.2 days; and hospital-wide: 276.9 days; 95% CI, 274.8–279.0 days). **Conclusions:** The DES model predicted that implementation of either universal suicide risk screening scenario would not severely impact LOS or wait times for BHC patients in our ED. However, universal screening would greatly stress our existing ED capacity to care for BHC patients in secure, dedicated patient areas by creating more overflow.

**Keywords:** Suicide, Mental Health, Emergency Department, Computer Simulation, Length of Stay

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## I. Introduction

### 1. Background

Suicide is the second leading cause of death among youth aged 10–24 years [1,2]. Effective July 1, 2019, the Joint Commission required suicide risk screening for all patients presenting to the emergency department (ED) with a behavioral health complaint (BHC) (National Patient Safety Goals [NPSG] 15.01.01) [3]. Among Medicaid-enrolled youth, nearly half of suicide decedents (44.8%, odds ratio of 2.87 compared to controls) had a healthcare visit in the month

# The History of Research Advocacy in Cerebral Palsy

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**Abstract:** Cerebral palsy (CP) is the most common motor disability of childhood, but US federal government investment into CP research has historically been under-prioritized and under-funded. This issue was brought to the forefront by the parent advocacy group Reaching for the Stars who partnered with the American Academy for Cerebral Palsy and Developmental Medicine to create a strong parent/professional partnership. This collaboration has resulted in increased awareness and federal commitment to cerebral palsy. This article highlights the important steps and lessons learned in the continuing journey of federal advocacy for CP research.

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*Case Report*

# Farber Disease Mimicking Juvenile Idiopathic Arthritis: The First Reported Case in Qatar and Review of the Literature

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Farber disease (FD) is an extremely rare autosomal recessive disorder caused by the deficiency of lysosomal acid ceramidase. It is characterized by a triad of progressive multiple joints' involvement, subcutaneous nodules, and hoarseness of voice. In this report, we describe a 23-month-old boy diagnosed with Farber disease. Initially, he was misdiagnosed as juvenile idiopathic arthritis (JIA) because he presented with joint swelling. However, the associated hoarseness of voice, subcutaneous nodules, and poor response to treatment all have questioned the diagnosis of JIA and prompted the suspicion of Farber disease as an alternative diagnosis. The diagnosis was later confirmed genetically by the presence of a homozygous pathogenic variant (p.Gly213Glu; c.638G > A in exon 8) in the ASAH1 gene. The present case illustrates the diagnostic journey of a child with Farber disease as well as highlights that FD should be considered in the differential diagnosis of early onset arthritis in the presence of subcutaneous nodules and/or hoarseness of voice.

## 1. Introduction

Farber disease (FD) is an extremely rare, inherited, progressive lysosomal storage disease that is characterized by subcutaneous nodules, arthralgia, and hoarseness of voice. Due to its rarity, it can be often misdiagnosed as juvenile idiopathic arthritis (JIA).

Hereby, we present a case of Farber disease in a child who was initially managed as JIA. Our case represents the first reported case in the state of Qatar and highlights the importance of considering such rare genetic disease entities, especially in the context of lack of improvement with conventional therapy.

## 2. Case Presentation

The patient is a 23-month-old boy with uneventful perinatal and postnatal history. He was referred to the pulmonology clinic with hoarseness of voice for the assessment of upper airway obstruction. His past medical history started at the age of 4 months with progressive hoarseness of voice and stridor. These symptoms were followed by swollen painful joints, predominantly in the hands and feet, in addition to poor weight gain. He was born to consanguineous parents of Indian descent with no family history of rheumatological or inherited disorders. Family sought medical advice at the age of 12 months. During the initial assessment in the pediatric clinic, the patient was found to have failure to thrive. His vital signs were stable, and he maintained oxygen saturation on room air. He had biphasic stridor with hoarse cry and intermittent subcostal retractions. The interphalangeal joints, wrists, knees, and ankles were swollen and tender with subcutaneous nodules on the wrist and ankles, as shown in Figure 1. There was no erythema or warmth. Bilateral hands' X-ray revealed soft tissue swelling of both distal hands with grossly maintained joint spaces. However,

# Amplitude-Integrated Electroencephalography: A Primer for Neonatologists and Practitioners in the NICU

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## EDUCATION GAPS

1. Neonatologists need to understand and interpret various patterns of amplitude-integrated electroencephalography (aEEG) patterns in both preterm and term infants.
2. Learning the indications, technical aspects, and limitations of aEEG should be a part of neonatal training programs.

## OBJECTIVES *After completing this article, readers should be able to:*

1. Describe the practical aspects of applying electroencephalography (aEEG) electrodes and avoiding impedance.
2. Explain the basics of aEEG, its various patterns, and their clinical implications.
3. Recognize various artifacts during aEEG monitoring to avoid misinterpretations.

## ABSTRACT

Amplitude-integrated electroencephalography (aEEG) is an essential tool used in the NICU to monitor infants with central nervous system pathology and encephalopathy. This review provides a summary of aEEG, including clinical indications, interpretation of different tracing patterns, and seizure identification, which are essential skills for teams caring for sick newborns. We also discuss the limitations of the clinical application of aEEG in this population.

**AUTHOR DISCLOSURES** Dr Durrani and Ms Dinan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

**ABBREVIATIONS**

| | |
|---|---|
| aEEG | amplitude-integrated electroencephalography |
| cEEG | conventional electroencephalography |
| CFM | cerebral function monitor |
| EEG | electroencephalography |
| SWC | sleep-wake cycle |

## INTRODUCTION

Amplitude-integrated electroencephalography (aEEG) is a valuable modality for continuously monitoring cerebral function in an intensive care setting. It was first described in 1960 by Maynard et al as a tool to monitor the intraoperative cerebral function of adults during anesthesia. (1) However, it did not gain much acceptance as the technology kept evolving and required constant recalibration. It gained favor in the 1980s when neonatologists reintroduced it for use in

Original Article

# Characteristics and outcomes of preoperatively treated patients with anaplastic Wilms tumors registered in the UK SIOP-WT-2001 and IMPORT study cohorts (2002-2020)

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**BACKGROUND:** Since the International Society of Paediatric Oncology Wilms' Tumour 2001 (SIOP-WT-2001) study, focal anaplastic Wilms tumors (FAWTs) have been treated as intermediate-risk Wilms tumors (WTs), and diffuse anaplastic Wilms tumors (DAWTs) have been treated as high-risk tumors. **METHODS:** The authors performed a retrospective analysis of preoperatively treated patients with FAWT or DAWT recruited in 2 consecutive UK Children's Cancer and Leukaemia Group WT studies. **RESULTS:** One hundred twenty-one of 1237 patients (10%) had an anaplastic WT confirmed by central pathology review (CPR): 93 (77%) had DAWT, and 28 (23%) had FAWT. The 4-year event-free survival (EFS) was 51% (95% confidence interval [CI], 41%-63%) for DAWT, 88% (95% CI, 76%-100%) for FAWT, and 84% (95% CI, 82%-87%) for intermediate-risk nonanaplastic Wilms tumor (IR-non-AWT). Overall survival (OS) was 58% (95% CI, 48%-70%) for DAWT, 95% (95% CI, 86%-100%) for FAWT, and 95% (95% CI, 93%-96%) for IR-non-AWT. In a multivariate analysis, the presence of DAWT was a significant prognostic factor for both EFS and OS in stages II, III, and IV. In a multivariate analysis of unilateral DAWT, stages III and IV remained the only significant prognostic factors for both EFS and OS. In 28% of the cases, there were discrepancies affecting the recognition of anaplasia, classification (DAWT vs FAWT), or the local pathologic stage. **CONCLUSIONS:** Preoperatively treated patients with FAWT had excellent outcomes in comparison with those with identically treated IR-non-AWT, whereas patients with DAWT showed significantly worse outcomes. All patients with stage I disease had comparable good outcomes, regardless of the presence/absence of anaplasia. In contrast, the presence of DAWT was associated with significantly worse outcomes for patients with stage II to V disease. Finally, significant diagnostic discrepancies emphasize the value of CPR. ***Cancer* 2022;128:1666-1675**. © *2022 American Cancer Society*.

**LAY SUMMARY:**

- Anaplasia is an unfavorable feature in Wilms tumor (WT), and it is classified as focal (focal anaplastic Wilms tumor [FAWT]) or diffuse (diffuse anaplastic Wilms tumor [DAWT]).
- This study reports the outcomes of patients with FAWT and DAWT who were, for the first time, treated differently.
- Patients with FAWT received less intensive treatment, and their outcomes were comparable to the outcomes of patients with identically treated nonanaplastic WT.
- Patients with stage I DAWT also had good outcomes when they were treated without radiotherapy, whereas patients with stage II to V DAWT had poor outcomes despite more intensive treatment.

**KEYWORDS:** diffuse anaplasia, focal anaplasia, outcomes, preoperative chemotherapy, Wilms tumor.

## INTRODUCTION

Anaplastic Wilms tumor (AWT) is a distinct type of Wilms tumor (WT) that is characterized by large, atypical, multipolar mitoses, marked nuclear enlargement, and hyperchromasia[1,2] and associated with *TP53* mutations.[3-6] It is classified as focal anaplasia (focal anaplastic Wilms tumor [FAWT]) or diffuse anaplasia (diffuse anaplastic Wilms tumor [DAWT]).[1,7] Anaplasia has been strongly associated with a poor prognosis in WT. In 2001, the International Society of Paediatric Oncology (SIOP) Renal Tumor Study Group introduced a new risk stratification in a prospective randomized trial and study International Society of Paediatric Oncology Wilms' Tumour 2001 (SIOP-WT-2001),[8] where FAWT was classified as an intermediate-risk Wilms tumor (IR-WT), but DAWT remained a high-risk tumor.

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# Characterizing the effective reproduction number during the COVID-19 pandemic: Insights from Qatar's experience

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**Background** The effective reproduction number, $R_t$, is a tool to track and understand pandemic dynamics. This investigation of $R_t$ estimations was conducted to guide the national COVID-19 response in Qatar, from the onset of the pandemic until August 18, 2021.

**Methods** Real-time "empirical" $R_t^{Empirical}$ was estimated using five methods, including the Robert Koch Institute, Cislaghi, Systrom-Bettencourt and Ribeiro, Wallinga and Teunis, and Cori et al. methods. $R_t$ was also estimated using a transmission dynamics model ($R_t^{Model\text{-}based}$). Uncertainty and sensitivity analyses were conducted. Correlations between different $R_t$ estimates were assessed by calculating correlation coefficients, and agreements between these estimates were assessed through Bland-Altman plots.

**Results** $R_t^{Empirical}$ captured the evolution of the pandemic through three waves, public health response landmarks, effects of major social events, transient fluctuations coinciding with significant clusters of infection, and introduction and expansion of the Alpha (B.1.1.7) variant. The various estimation methods produced consistent and overall comparable $R_t^{Empirical}$ estimates with generally large correlation coefficients. The Wallinga and Teunis method was the fastest at detecting changes in pandemic dynamics. $R_t^{Empirical}$ estimates were consistent whether using time series of symptomatic PCR-confirmed cases, all PCR-confirmed cases, acute-care hospital admissions, or ICU-care hospital admissions, to proxy trends in true infection incidence. $R_t^{Model\text{-}based}$ correlated strongly with $R_t^{Empirical}$ and provided an average $R_t^{Empirical}$.

**Conclusions** $R_t$ estimations were robust and generated consistent results regardless of the data source or the method of estimation. Findings affirmed an influential role for $R_t$ estimations in guiding national responses to the COVID-19 pandemic, even in resource-limited settings.

CORRESPONDENCE

# Protection against the Omicron Variant from Previous SARS-CoV-2 Infection

**TO THE EDITOR:** Natural infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) elicits strong protection against reinfection with the B.1.1.7 (alpha),[1,2] B.1.351 (beta),[1] and B.1.617.2 (delta)[3] variants. However, the B.1.1.529 (omicron) variant harbors multiple mutations that can mediate immune evasion. We estimated the effectiveness of previous infection in preventing symptomatic new cases caused by omicron and other SARS-CoV-2 variants in Qatar. In this study, we extracted data regarding coronavirus disease 2019 (Covid-19) laboratory testing, vaccination, clinical infection data, and related demographic details from the national SARS-CoV-2 databases, which include all results of polymerase-chain-reaction (PCR) testing, vaccinations, and hospitalizations and deaths for Covid-19 in Qatar since the start of the pandemic.

The effectiveness of previous SARS-CoV-2 infection in preventing reinfection was defined as the proportional reduction in susceptibility to infection among persons who had recovered from infection as compared with those who had not been infected.[4] Previous SARS-CoV-2 infection was defined as a positive result on PCR assay at least 90 days before a new positive PCR finding.[4] We used a test-negative, case–control study design to assess the effectiveness of previous infection in preventing reinfection on the basis of a method that had recently been investigated and validated for derivation of robust estimates for such comparisons[4] (Section S1 of the Supplementary Appendix, available with the full text of this letter at NEJM.org). In addition, we performed sensitivity analyses that included adjustment for vaccination status and that excluded vaccinated persons from the analysis. Case patients (defined as persons with positive PCR results) and controls (defined as persons with negative PCR results) were matched according to sex, 10-year age group, nationality, and calendar time of PCR testing to control for known differences in the risk of exposure to SARS-CoV-2 infection in Qatar.[4]

To ensure that epidemiologically relevant reinfections were considered in the analysis, only documented infections with a PCR cycle threshold (Ct) value of 30 or less were included as cases in our study. (Reinfection often occurs with negligible symptoms and high Ct values, indicating reduced epidemiologic significance.)[5] We also estimated the effectiveness of previous infection in preventing hospitalization or death caused by reinfection.

The selection of the study population for various analyses is shown in Figures S1 through S4 and the population characteristics in Tables S1 and S2. The overall study population was broadly representative of the total population of Qatar (Table S3), with a median age of 31 to 35 years across the study samples. The median interval between previous infection and PCR testing among cases and controls was 279 days (interquartile range [IQR], 194 to 313) for analysis of the alpha variant, 285 days (IQR, 213 to 314) for analysis of the beta variant, 254 days (IQR, 159 to 376) for analysis of the delta variant, and 314 days (IQR, 268 to 487) for analysis of the omicron variant.

The effectiveness of previous infection in preventing reinfection was estimated to be 90.2% (95% confidence interval [CI], 60.2 to 97.6) against the alpha variant, 85.7% (95% CI, 75.8 to 91.7) against the beta variant, 92.0% (95% CI, 87.9 to 94.7) against the delta variant, and 56.0% (95% CI, 50.6 to 60.9) against the omicron variant (Table 1). Sensitivity analyses confirmed the study results, as expected for this study design, which is robust regardless of the approach that is used to control for vaccine-induced immunity.[4] An additional analysis that was adjusted for the interval since previous infection also confirmed the study results (Table S4).

Among the patients with reinfection, progression to severe Covid-19 occurred in one patient

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CASE REPORT

# Homozygous Insulin Promotor Gene Mutation Causing Permanent Neonatal Diabetes Mellitus and Childhood Onset Autoantibody Negative Diabetes in the Same Family

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**Purpose:** To report a family with a homozygous INS promotor gene mutation causing permanent neonatal diabetes mellitus (PNDM) in one sibling and autoantibody negative childhood onset diabetes in another sibling.

**Case Presentation:** Patient 1 is a 12-year-old girl born at term with low birth weight to a consanguineous family, diagnosed with PNDM at 26 days of life. She presented with ketoacidosis and has a severe course of disease with high insulin requirement. Patient 2 is a 9-year-old girl born at term with normal weight, who presented with ketoacidosis at 2 years of age. Both subjects have negative type 1 autoantibodies. On genetic testing, a mutation in the promoter region of INS gene c.-331 C>G was found in homozygous state in both subjects and in a heterozygous state in parents.

**Conclusion:** Homozygous INS gene promotor mutations may present with either PNDM or later onset autoantibody negative diabetes in childhood. This suggests that homozygous INS gene promotor mutations show marked heterogeneity in clinical presentation within individuals in the same family. The pathophysiology of this is not well known but could be related to a number of factors, including the position of the variant, penetrance, other associated genetic defects, HLA etc. Premarital screening and genetic counselling is recommended for highly consanguineous families to reduce occurrence of such conditions.

**Keywords:** pediatric diabetes, neonatal diabetes mellitus, type 1b diabetes, INS mutation

## Introduction

Neonatal diabetes mellitus is defined as hyperglycemia occurring in the first 6 months of life. It is a rare condition with a minimal incidence of 1 in 90,000 live births; however, variations have been reported in various ethnic groups.[1] There are two main types of neonatal diabetes: permanent neonatal diabetes mellitus (PNDM) and transient neonatal diabetes mellitus (TNDM). The causes of PNDM vary around the world but the most common cause in the Western world is due to mutations in the genes (*ABCC8/KCNJ11*) coding for the SUR1 and KIR6.2 subunits of the potassium ATP channels, respectively.[2] Insulin promotor gene (INS) mutations are a rare cause of PNDM.[3] Both heterozygous and homozygous INS promotor gene mutations may lead to PNDM.

Heterozygous INS promotor gene mutations were first reported to cause neonatal diabetes in 2007 where 10 mutations in 16 probands with neonatal diabetes were reported.[3] Subsequently, many more variants have been reported. The mechanism of diabetes in heterozygous mutations is due to improper folding of proinsulin, which leads to endoplasmic reticulum stress and beta cell apoptosis.[4] In addition, homozygous INS promotor gene mutations were first reported in 2010 in 15 probands with neonatal diabetes.[5] The mechanism of diabetes in homozygous INS mutations

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VIEWPOINT

Cosmetic

# Next-generation Septal Contouring in Aesthetic Rhinoplasty: A Structural Viewpoint

**Graeme E. Glass, PhD, FRCS (Plast)*†; Lydia Badia, MD, FRCS‡§; Charles A. East, MD, FRCS‡§**

Aesthetic rhinoplasty is a challenge of both architecture and engineering. While aesthetic appeal is conspicuous, sound geometric design, even load distribution, and foundational stability are the concealed principles of durable results. Additional challenges faced by the rhinoplasty surgeon include complex material properties, variable boundary conditions, and irregular stresses.[1]

Septal cartilage remains the prime source of graft material in aesthetic rhinoplasty. Surgical pioneers including Ingals (1882), Kreig (1889), Freer (1902), and Killian (1905) advocated preservation of the dorsal and caudal extent of the septum—a configuration that has become known as the "L-strut."[2] Oral tradition advocates preservation of dorsal and caudal limbs of 10–15 mm width. However, borrowing from the foundations to adorn the façade is structurally dubious while cartilage yield correlates poorly with external nasal projection.[3] Problematically, the L-strut comprises the thinnest portions of the septum yet supports the lower two-thirds of the nose. Structural failure causes nasal collapse, saddle deformity, tip deviation, and nasal valve dysfunction. Warping or fracture of the thin right angle is encountered in up to 40% of revision surgeries.[4]

Curiously, the structural competence of a right angled L-strut evaded scrutiny until recently. This probably reflects the sense of rigor and purpose with which the modern rhinoplasty community are reappraising their craft to meet heightened functional and aesthetic expectations.[5] In 2007, human cadaveric septal L-struts were first investigated by finite element modeling to better understand surgical failure.[6] Subsequent investigations added greater complexity and sophistication to the understanding of L-strut biomechanics and how failure might be mitigated through improved surgical design.[7] Our assimilation of the collective computational evidence supports the replacement of the L-strut with a delta-shaped strut.[1]

It is interesting to speculate on the reasons for the enduring appeal of the L-strut. There is inevitably a learning curve when faced with a paradigm shift, and thus, a powerful motivator for change is necessary. Many of us who have embraced an approach based on structural preservation have done so only after stepping out of the comfort zone when faced with the evidence from our own clinical observations. Moreover, as aestheticians rather than bioengineers, we are averse to analyzing structural failure from a mathematical point of view.

The philosophy of structural optimization has merged with the trends toward elevation of the soft tissue envelope in the subperichondrial/subperiosteal plane, preservation of the nasal dorsum, and advances in suture-based manipulation of the lower lateral cartilages into a new philosophical approach to primary aesthetic rhinoplasty.[8] These founding principles are risk-averse in that they preserve the structural integrity of the nose, avoiding the need for complex reconstructive rhinoplasty for primary failures.[5]

Thus, although the tenacious popularity of the L-strut is acknowledged, it is hard to justify from a structural point of view. Rather, the computationally sound "delta strut," with optimized axial load distribution and foundational stability, is better placed to support aesthetic remodeling and withstand the vicissitudes of time. As preservation techniques gain traction within the rhinoplasty community, the preeminence of the L-strut will become increasingly challenged until a new paradigm is established.

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*This article does not contain any studies with human participants or animals performed by any of the authors. For this type of study, informed consent is not required.*

## DISCLOSURE

*G.E. Glass is a member of the British Association of Aesthetic Plastic Surgeons. All the authors have no financial interest to declare in relation to the content of this article.*

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Letter to the Editor

# A unique technique to size pediatric endotracheal tubes

*To the Editor,*

Pediatric airway anatomy is different from adults. The larynx is shorter and more anteriorly located.[1] There are different formulas to estimate the size of endotracheal tubes (ETT) in pediatric population based on ages, such as Cole (Age/4 + 4), Khine (age/4 + 3) and Duracher (Age/4 + 3.5) formulas.[2,3] Among these, Duracher formula provides better estimates of the sizes of cuffed ETT in children over 1 years of age.[3] In emergency and trauma settings, sometimes it is cumbersome to calculate ETT sizes using the above formulas. So, we present a technique to remember ETT sizes for different ages as below

- 3.5 mm at birth
- 4.5 mm at 4 years
- 5 mm at 5 years (then increase the size of tube by 1 mm for every 5 years)
- 6 mm at 10 years
- 7 mm at 15 years

This technique does not provide tube sizes for all ages. Rather it provides a reference point from which tube sizes for other ages can be approximately estimated. For example, for ages 7–8 years we can use ETT size 5.5 mm. Similarly for ages 12–13 years we can use the ETT size 6.5 mm.

The advantage of this technique is that it's easy to remember and can be readily used in crashing patients without going through calculations. The limitation of this technique is that it may underestimate or overestimate the size of ETT by 0.25 mm compared to the Duracher formula. (Table 1) Also this technique has not been formally studied.

**Table 1 – Comparison of ETT sizes estimated using our technique and Duracher formula.**

| Ages | Our Technique | Duracher Formula |
|---|---|---|
| Birth | 3.5 | N/A |
| 4 years | 4.5 | 4.5 |
| 5 years | 5 | 4.75 |
| 10 years | 6 | 6 |
| 15 years | 7 | 7.25 |

## Conflict of interest

We report no conflict of interest.

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RAPID COMMUNICATION



# Anosmia (smell failure) and dysgeusia (taste distortion) in COVID-19: it is genetic

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**ABSTRACT**

The COVID-19 pandemic is a very contagious respiratory illness with has affected millions of individuals worldwide. In addition to the well-known symptoms of any respiratory virus, COVID-19 can present with anosmia (failure to smell) and dysgeusia (distortion of the sense of taste). It appears to be a genetic link to the biological mechanisms underlying COVID-19-related anosmia and dysgeusia. Significant locus in the vicinity of the UGT2A1 and UGT2A2 genes are currently considered as the main culprit of the symptoms. However, more studies are needed to delineate a clear pathophysiology.

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**KEYWORDS**
Anosmia; COVID-19; dysgeusia

## Introduction

The COVID-19 pandemic is a very contagious respiratory illness with effects that have been undesirable to global health, society, and economy (Hendaus & Jomha, 2021).

The world health organization (WHO) has reported 340,543,962 confirmed cases of COVID-19, including 5,570,163 deaths as of January 21, 2022. In addition, more than 9.5 Billion vaccines have been given (WHO, 2022). In addition to the well-known symptoms of any respiratory virus, COVID-19 can present with anosmia (failure to smell) and dysgeusia (distortion of the sense of taste) (Marinosci et al., 2020).

Dysgeusia is a sensory estate of losing taste discernment (Mutiawati et al., 2021), while anosmia (failure to smell) is a severe condition of hyposmia (a decreased capability of smelling) . It reflects a part of olfactory dysfunction where an individual cannot detect odor or cannot properly smell. This condition has a prevalence of around 15 of every 1000 people in the United States (prior to the COVID-19 pandemic) (Huynh et al., 2020). However, the prevalence of smelling and tasting dysfunction in COVID-19 patients can reach to 33.5 and 35.6%, respectively (Galluzzi et al., 2021), and the two symptoms have affected approximately 1.6 million Americans for longer than six months the initial infection with SARS-Cov-2 (Khan et al., 2022).

The loss of vital senses has been linked with changes in appetite and quality of life. Moreover, it can decrease the ability to detect harmful smoke or gases, aggravate worries about personal hygiene and can decrease social interaction (Arora et al., 2008; Croy et al., 2014).

Current data has shown a possible association between a genetic risk factor and anosmia/dysgeusia post- COVID-19 infection. Shelton et al (Shelton et al., 2022) reported a genome-wide significant locus in the vicinity of the *UGT2A1* and *UGT2A2* genes in COVID-19 patients with anosmia/dysgeusia. The investigators conducted a multi-ancestry genome-wide association study on 69,841 person infected with SARS-CoV-2. Approximately 70% of them reported anosmia or dysgeusia, and genetic investigation resulted in pinpointing locus *UGT2A1* and *UGT2A2* to be linked to COVID-19-related anosmia/dysgeusia.

## Uridine diphosphate glucuronosyltransferases (UGTs)

Several medications and non-drug xenobiotics, such as dietary, environmental, dietary and industrial chemicals, are nonpolar, lipophilic compounds. The lipophilic characteristic of those compounds hampers their proper excretion from the body. Hence, they require metabolism to be changed from lipophilic estate to hydrophilic and then excretion (Rowland et al., 2013). Glucuronidation catalyzed by uridine diphosphate glucuronosyltransferases (UGTs) is one of the most important xenobiotic metabolism mechanisms. UGTs can generate the conjugation of glucuronic acid to hydrophilic substances for excretion, such as bile acids and hormones (Kiang et al., 2005). The UGT membrane proteins are

CONTACT Mohamed A. Hendaus mhendaus@yahoo.com Department of Pediatrics, Sidra Medicine, Doha, Qatar 26999.
Comments by Editor-In-Chief: This article by Mohamed A. Hendaus, MD., FAAP., Clinical Pediatrics Weill Cornell Medicine, Doha, Qatar, is a simplified account of the reasons for smell failure and taste distortion in COVID patients. It is written and illustrated in such a way that any interested structural biologist, including doctoral students could understand it. The article does not present any new information to specialists who are already working in the area of COVID-19.

# The re-occurrence of dilated cardiomyopathy in propionic acidemia after liver transplantation requiring heart transplant, first case from Middle East

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Affiliations + expand

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## Abstract

Propionic acidemia is a rare autosomal recessive inborn error of metabolism. It is relatively common in Middle East. Dilated cardiomyopathy is one of the leading causes of morbidity and mortality for patients with propionic acidemia. Liver transplantation has been used for patient with frequent metabolic decompensations and was shown to be beneficial in propionic acidemia-related dilated cardiomyopathy. Up to our knowledge, there has been one reported case of recurrent dilated cardiomyopathy 3 years after liver transplantation. We report the first case, from Middle East, of recurrent dilated cardiomyopathy, 6 years after liver transplantation.

**Keywords:** Propionic acidemia; dilated cardiomyopathy; inborn error of metabolism; liver transplantation.

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# QCovSML: A reliable COVID-19 detection system using CBC biomarkers by a stacking machine learning model

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ABSTRACT

The reverse transcription-polymerase chain reaction (RT-PCR) test is considered the current gold standard for the detection of coronavirus disease (COVID-19), although it suffers from some shortcomings, namely comparatively longer turnaround time, higher false-negative rates around 20–25%, and higher cost equipment. Therefore, finding an efficient, robust, accurate, and widely available, and accessible alternative to RT-PCR for COVID-19 diagnosis is a matter of utmost importance. This study proposes a complete blood count (CBC) biomarkers-based COVID-19 detection system using a stacking machine learning (SML) model, which could be a fast and less expensive alternative. This study used seven different publicly available datasets, where the largest one consisting of fifteen CBC biomarkers collected from 1624 patients (52% COVID-19 positive) admitted at San Raphael Hospital, Italy from February to May 2020 was used to train and validate the proposed model. White blood cell count, monocytes (%), lymphocyte (%), and age parameters collected from the patients during hospital admission were found to be important biomarkers for COVID-19 disease prediction using five different feature selection techniques. Our stacking model produced the best performance with weighted precision, sensitivity, specificity, overall accuracy, and F1-score of 91.44%, 91.44%, 91.44%, 91.45%, and 91.45%, respectively. The stacking machine learning model improved the performance in comparison to other state-of-the-art machine learning classifiers. Finally, a nomogram-based scoring system (QCovSML) was constructed using this stacking approach to predict the COVID-19 patients. The cut-off value of the QCovSML system for classifying COVID-19 and Non-COVID patients was 4.8. Six datasets from three different countries were used to externally validate the proposed model to evaluate its generalizability and robustness. The nomogram demonstrated good calibration and discrimination with the area under the curve (AUC) of 0.961 for the internal cohort and average AUC of 0.967 for all external validation cohort, respectively. The external validation shows an average weighted precision, sensitivity, F1-score, specificity, and overall accuracy of 92.02%, 95.59%, 93.73%, 90.54%, and 93.34%, respectively.

## 1. Introduction

After only one year and a half years' duration of the pandemic, the SARS-CoV2 coronavirus, the pathogen responsible for COVID-19, has caused about 360 million infections with over five million casualties around the globe [1]. It is the worst pandemic that afflicted humanity

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children

MDPI

*Case Report*

# Use of Intravenous Pulse Steroids to Treat Allergic Bronchopulmonary Aspergillosis in a Non-Compliant Asthmatic Adolescent

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**Abstract:** Allergic bronchopulmonary aspergillosis (ABPA) is an immune-mediated inflammatory airway disease that predominantly affects patients with cystic fibrosis (CF) and, less commonly, patients with asthma. ABPA can lead to irreversible lung injury and bronchiectasis if not treated early and aggressively. Long-term oral steroids are the standard therapy of ABPA. However, it is associated with an increased risk of steroids side effects and possible medication noncompliance. Monthly intravenous pulse methylprednisolone (IV-PS) has been used as an alternative to oral steroids to treat CF-related ABPA with a reportedly similar clinical response and less steroid-related side effects. To our knowledge, the use of IV-PS in asthma-related ABPA has not been previously reported. We report the successful management of asthma-related ABPA in an adolescent using intravenous pulse methylprednisolone in addition to oral itraconazole with no significant steroid-related side effects.

**Keywords:** allergic bronchopulmonary aspergillosis (ABPA); asthma; pulse steroids



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## 1. Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is an immune-mediated inflammatory airway disease that predominantly affects patients with cystic fibrosis (CF) and, less commonly, patients with asthma [1,2]. Long-term oral steroids are the standard therapy of ABPA. However, it is associated with an increased risk of steroid side effects and possible medication noncompliance. Monthly intravenous pulse methylprednisolone (IV-PS) has been used as an alternative to oral steroids to treat CF-related ABPA with a reportedly similar clinical response and less steroid-related side effects. To our knowledge, the use of IV-PS in asthma-related ABPA has not been previously reported.

We report the successful management of asthma-related ABPA in an adolescent using intravenous pulse methylprednisolone in addition to oral itraconazole with no significant steroids related side effects.

## 2. Case Presentation

The patient is a 14-year-old boy with asthma who was admitted with mild right pleuritic chest pain and an increased productive cough of a one-month duration. The cough became productive of yellow-greenish sputum and did not respond to an inhaled bronchodilator. The patient reported no wheezing, shortness of breath, hemoptysis, weight loss, nor fever of chills.

The past medical history was significant for mild persistent asthma since the age of 3 years which required multiple emergency department visits, but no hospital or PICU admissions. He has poor adherence to controller inhaled steroid treatment, especially over the past 3 years. On physical examination, the patient had normal vital signs and normal

sensors

MDPI

*Article*

# Thermal Change Index-Based Diabetic Foot Thermogram Image Classification Using Machine Learning Techniques

**Amith Khandakar [1,2], Muhammad E. H. Chowdhury [1,*], Mamun Bin Ibne Reaz [2,*], Sawal Hamid Md Ali [2], Tariq O. Abbas [3], Tanvir Alam [4], Mohamed Arselene Ayari [5], Zaid B. Mahbub [6], Rumana Habib [7], Tawsifur Rahman [1], Anas M. Tahir [1], Ahmad Ashrif A. Bakar [2] and Rayaz A. Malik [8]**

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**Abstract:** Diabetes mellitus (DM) can lead to plantar ulcers, amputation and death. Plantar foot thermogram images acquired using an infrared camera have been shown to detect changes in temperature distribution associated with a higher risk of foot ulceration. Machine learning approaches applied to such infrared images may have utility in the early diagnosis of diabetic foot complications. In this work, a publicly available dataset was categorized into different classes, which were corroborated by domain experts, based on a temperature distribution parameter—the thermal change index (TCI). We then explored different machine-learning approaches for classifying thermograms of the TCI-labeled dataset. Classical machine learning algorithms with feature engineering and the convolutional neural network (CNN) with image enhancement techniques were extensively investigated to identify the best performing network for classifying thermograms. The multilayer perceptron (MLP) classifier along with the features extracted from thermogram images showed an accuracy of 90.1% in multi-class classification, which outperformed the literature-reported performance metrics on this dataset.

**Keywords:** diabetic foot; thermogram; thermal change index; machine learning; deep learning

## 1. Introduction

Diabetes mellitus (DM) is characterized by hyperglycemia which can lead to pathology in the brain, heart, eyes, kidney's and lower limbs [1]. DM leads to diabetic foot ulceration (DFU), which may not heal adequately due to poor microvascular and macrovascular tissue perfusion and infection and may eventually lead to lower limb amputation [2,3]. Early detection and better classification of foot complications may enable timely intervention and effective treatment to either heal foot ulcers or prevent progression to amputation. Early monitoring by self-diagnosis at home could be useful in preventing the development and progression of DFU. However, the easiest monitoring technique, visual inspection, has its limitations, for example, people with obesity or visual impairment cannot adequately detect early changes. According to recent studies, a home temperature monitoring system could detect 97% of diabetic foot ulcers (DFUs) well in advance [4–7]. Patients undergoing continuous temperature monitoring of their feet have a lower risk of foot complications [8].

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# Covid-19 and its implications for the provision of gynecological services globally

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ABSTRACT

Covid-19 took the world by surprise and has completely changed the way humans live and work. There is hardly an aspect of life that has not been affected. Whether social, economic, physical, psychological, cultural or religious, this pandemic has revolutionized every aspect of our lives and some of these changes are here to stay for the unforeseeable time. Although much has been written about the negative effects of Covid-19 on our social lives, some technological advances on COVID-19 have profoundly affected various aspects of our lives. These are mostly to do with how we communicate, deliver health services, innovate and investigate new preventative measures and treatments, travel and indeed influenced the carbon footprint of the planet. Although most of gynaecology is elective and was therefore not considered a priority in the early phases of COVI-19, there are considerable consequences of delaying treatment for some of these elective conditions. Of particular importance are infertility, pre-malignant conditions, chronic pelvic pain, sexual disorders and those affecting the psychological and social aspects of women and families. The pandemic forced a rethink of how healthcare is delivered with wide adoption of remote/virtual consultation and triaging of clinical presentations. The rapid development of immunization and drugs against the virus was met with doubts by a large proportion of the population with reluctance to accept these. Consequently, there remains unvaccinated portions of both low and high-risk populations, some of whom may be denied access to gynaecological care. On the other hand, some pregnant women who are frightened of the impact of vaccination on pregnancy put their own lives at risk. While significant progress has been made to combat the pandemic, lessons about healthcare delivery (face-to-face versus virtual), education of the end users and introduction of new technologies into the development of drugs and vaccines must be evaluated and improved moving forward not only during the ongoing epidemic but with future outbreaks.

## Introduction

Corona viruses have generally been the cause of various infections in mammals, birds and humans, where they specifically target the respiratory system. Over the past 20 years, there have been three new corona virus related lethal outbreaks of zoonotic origin. The 1st was the severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) in 2002–2003 followed by the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 and lately, the most severe of them, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing the 2020 March Covid-19 pandemic [1,2]

SARS-CoV-2 spread very rapidly after the first reported case of pneumonia like disease of unknown origin at the time, from a seafood and live animal market in Wuhan city, China, in late December 2019 [3]. Human respiratory epithelial cells were subsequently used to isolate a new virus subsequently known to the world as SARS-CoV-2. The World Health Organization (WHO) declared the outbreak as a Public Health Emergency of International Concern (PHEIC) on January 30th 2020 and subsequently as a pandemic on March 11th 2020 [4]. More than 5.7 million deaths have been reported worldwide (as of February 4, 2022) [5]. Three major factors are thought to be responsible for this (a) increased transmissibility (b) characteristic pathogenicity and (c) globalization [6,7].

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# Quality of Neonatal Care: A Health Facility Assessment in Balochistan Province, Pakistan

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## Abstract

### Introduction

Balochistan is the largest of Pakistan's four provinces, yet it is also the poorest and most impoverished, particularly in terms of neonatal healthcare. In order to build and tailor strategies to improve neonatal outcomes, it is necessary to identify barriers and facilitators for interventions. Therefore, we conducted this study to provide an overview of neonatal healthcare quality and assess the structural capacity for the improvement and further development of neonatal healthcare facilities in Balochistan.

### Methods

A descriptive, observational, cross-sectional study was conducted in Balochistan, a province of Pakistan. The survey was designed to assess the level of staffing and facilities in the neonatal health care units. Data were gathered through trained staff either by in-person visits to the facility or via telephone.

### Results

A total of 177 facilities were assessed in 25 districts of Balochistan. A majority (88.7%) of the facilities were from the public sector. Birth and neonatal care services were provided at only 63 (36%) of the assessed facilities and only three had newborn intensive care units (NICUs) with a 1:5 staff: patient ratio. Unfortunately, all NICUs lacked the basic advanced facilities. None of the hospitals had an infection control policy or staff nor any training program for doctors.

### Conclusion

In conclusion, healthcare facilities to manage neonatal patients requiring hospital care are extremely limited in Balochistan and the ones that are available have very limited resources. To improve the healthcare system in Balochistan, all stakeholders should be involved in the planning, decision-making, and implementation of healthcare programs at all levels to ensure sustainability and efficiency.

**Categories:** Quality Improvement, Public Health, Other
**Keywords:** pakistan, balochistan, quality patient care, neonatal health, health facility

## Introduction

According to the United Nations Children's Fund (UNICEF), at least 130 million infants are born each year, of which approximately 2.4 million children die within the first 28 days of life, accounting for roughly half of all child deaths under the age of five [1-2]. More than 90% of these fatalities occur in developing countries, primarily in Sub-Saharan Africa and South Asia, whereas in 2019, the neonatal mortality rate was estimated at 25-27 deaths per 1,000 live births [1,3]. An infant born in a developing country is 10 times more likely to die in the first month than an infant born in a developed country [4]. Pakistan ranks third among these developing countries with an estimated 298 000 neonatal deaths per year and a neonatal mortality rate (NMR) of 42 deaths per 1000 live births annually [5-6]. Pakistan accounts for 7% of neonatal deaths globally, with birth asphyxia (23%), infection (36%), and preterm birth (28%) as prime causes, all of which are preventable [5].

In Pakistan, marked disparities exist in the chances of survival for infants based on their provinces, regions (urban or rural), and district of birth. Among the four provinces of Pakistan, Balochistan is the largest but the poorest and most deprived of all. Despite being the least populated, it has the highest burden of neonatal mortality, i.e., 63 deaths per 1000 live births [7]. Surprisingly, this rate is comparable to Punjab, one of the most populous provinces in the country. The most prominent factors contributing to the alarming neonatal mortality rate are lack of postnatal care for infants within 48 hours, poor maternal breastfeeding habits, and immunization follow-ups. Other causes include premature birth complications, intrapartum complications,

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# Hemodynamic management of the micropreemie: When inotropes are not enough

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ABSTRACT

Managing perfusion in the micropreemie is challenging and should be guided by the patho-physiology, gestational and postnatal age of the baby, perinatal history, and the persistence of fetal shunts. The assessment should incorporate bedside tools such as blood pressure, clinical perfusion markers, and functional echocardiography. The multimodal approach to diagnose and identify the cause of hemodynamic compromise paves the way to a targeted approach to treatment. Characterizing the predominant pathophysiologic cause of low cardiac output and impaired cellular metabolism enables a more accurate use of inotropes, vasopressors, and volume support to suit a particular pathophysiologic situation.

## 1. Introduction

The hemodynamic challenges of the micropreemie primarily result from immaturity of the circulatory system. As the premature infant transitions to extrauterine life before fetal circulation has matured, the infant will continue to manifest structural and functional characteristics and therefore, consequences of persisting fetal vasculature.

## 2. Transitional circulation and the micropreemie

With premature birth, the normal postnatal adaptation of circulation and transition from fetal to postnatal life is disrupted. The key features are:

- *Poor contractility of the myocardium* - The circulatory triad of cardiac physiology is preload, contractility, and afterload. The *preload* affects the stretching of cardiac muscle fibers before contraction and is dependent upon the number of actin-myosin bridges, which help in the generation of force. The recent work on 'titin' (connecting) protein has highlighted its role in myocyte function. It links the Z-disc region of thin filament to myosin thick filament, allowing it to stretch and also mediate force generation by altering $Ca^{2+}$ release. Additionally, the *contractility* of the heart is governed by the interaction of sympathetic and parasympathetic components of the autonomic nervous system. As the ejection time of blood is relatively constant, the volume of blood ejected by the ventricles is dependent upon the ejection velocity, which in turn depends upon force of contraction, and is mediated by intracellular calcium concentrations [1,2]. The immature myocardium's impaired contractility results from decreased fraction of contractile elements, immature pathways of calcium release, reduced titin function, reduced β-adrenoceptor, and decreased sympathetic innervation.
- *High systemic vascular resistance and tolerance* - With the increase in afterload from the fetal placental vascular bed to the postnatal high systemic vascular resistance (SVR), the wall stress within the ventricles increases affecting the rate at which muscle fibers contract and decrease the ejection volume. With umbilical cord clamping, both left and right ventricles face sudden increases in vascular resistance (Fig. 1). Additionally, high alpha-adrenergic resting tone in peripheral vasculature increases SVR, and in turn afterload, with its adverse effects on the immature myocardium [2].
- *Impaired diastolic filling* – In micropreemies, the diastolic filling is affected by the low compliance of fetal isoforms of titin, reduced diastolic filling time from the high heart rate, and the reliance of ventricular filling on atrial contraction (E/A <1.0). The use of inotropes further increases the heart rate, which in turn reduces diastolic filling time [3].

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SYSTEMATIC REVIEW
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# Accuracy and Trending Ability of Electrical Biosensing Technology for Non-invasive Cardiac Output Monitoring in Neonates: A Systematic Qualitative Review

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**Background:** Electrical biosensing technology (EBT) is an umbrella term for non-invasive technology utilizing the body's fluctuating resistance to electrical current flow to estimate cardiac output. Monitoring cardiac output in neonates may allow for timely recognition of hemodynamic compromise and allow for prompt therapy, thereby mitigating adverse outcomes. For a new technology to be safely used in the clinical environment for therapeutic decisions, it must be proven to be accurate, precise and be able to track temporal changes. The aim of this systematic review was to identify and analyze studies that describe the accuracy, precision, and trending ability of EBT to non-invasively monitor Left ventricular cardiac output and/or stroke volume in neonates.

**Methods:** A qualitative systematic review was performed. Studies were identified from PubMed NCBI, SCOPUS, and EBSCOHost up to November 2021, where EBT technologies were analyzed in neonates, in comparison to a reference technology. Outcome measures were bias, limits of agreement, percentage error for agreement studies and data from 4-quadrant and polar plots for trending studies. Effect direction plots were used to present results.

**Results:** Fifteen neonatal studies were identified, 14 for agreement and 1 for trending analysis. Only thoracic electrical biosensing technology (TEBT), with transthoracic echocardiography (TTE) as the comparator, studies were available for analyzes. High heterogeneity existed between studies. An equal number of studies showed over- and underestimation of left ventricular output parameters. All studies showed small bias, wide limits of agreement, with most studies having a percentage error >30%. Sub-analyses for respiratory support mode, cardiac anomalies and type of technology showed similar results. The single trending study showed poor concordance, high angular bias, and poor angular concordance.

**Discussion:** Overall, TEBT shows reasonable accuracy, poor precision, and non-interchangeability with TTE. However, high heterogeneity hampered proper analysis.

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# The impact of obesity on polytraumatized patients with operatively treated fractures

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ABSTRACT

*Introduction:* The objective of this study was to evaluate the effect of obesity on outcomes following operative treatment of fractures in obese polytrauma patients.
*Methods:* This was a prospective cohort study at a level I trauma centre from January 2014 until December 2017. The eligibility criteria were adult (age >= 18 years) polytrauma patients who presented with at least one orthopaedic fracture that required operative fixation. Polytrauma was defined as having an Injury Severity Score (ISS) >= 16. Out of 891 patients, a total of 337 were included with 85 being obese. The primary outcome variable was the total hospital length of stay in days. The secondary outcome variables were the number of patients who had an intensive care unit (ICU) admission, the ICU length of stay in days, the number of patients who had mechanical ventilation, the duration of mechanical ventilation in days, perioperative complications, and mortality.
*Results:* Obesity was associated with increased total hospital stay (36 vs. 27 days; $P<0.001$), increased ICU stay (13 vs. 8 days; $P = 0.04$), increased ICU admissions (83.5% vs. 68.6%; $P = 0.008$) and increased incidence of mechanical ventilation (64.7% vs. 43.7%; $P = 0.001$). These findings remained statistically significant following adjusted regression models for age, gender, ISS, and injuries sustained. However, the mechanical ventilation duration was not significantly different between both groups on adjusted and unadjusted analyses. However, an increase per unit BMI significantly increases the duration of mechanical ventilation ($P = 0.02$). In terms of complications, obesity was only associated with an increase in acute renal failure (ARF) on unadjusted analyses ($P = 0.004$). Whereas, adjusted logistic regression demonstrated that an increase per BMI unit led to a significant increase in the odds ratio for wound infection ($P = 0.03$) and ARF ($P = 0.024$).
*Conclusions:* This study displayed that obesity was detrimental to polytrauma patients with operatively treated fractures leading to prolonged hospital and ICU length of stay. This highlights the importance of optimizing trauma care for obese polytraumatized patients to reduce morbidity. With 41.1% of our population being obese, obesity presents a unique challenge in the care of polytrauma patients which mandates further research in improving health care for this population group.


## Introduction

Obesity is considered one of the major global health issues that are on the rise. Since 1975, it has been estimated that the prevalence of worldwide obesity has increased by 3-folds as of 2016 [1]. A significant proportion of the world's society is burdened by obesity; with 13% of the world's adult population being affected [2]. Obesity is associated with increased morbidity such as metabolic syndrome, diabetes, and cardiovascular disease; therefore, it imposes a significant burden on the health care system [3]. It has been reported in the United States that obesity-related health care resulted in a cost of $147 billion [4]. In a systematic review on the economic effect of obesity, Withrow and Alter [5] found that obese individuals had a 30% increase in health care costs compared to

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Review Article

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# Burden of Early Life Obesity and Its Relationship with Protein Intake in Infancy: The Middle East Expert Consensus

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## ABSTRACT

Adequate nutrition in early life is proposed to shape a child's future health by launching the growth trajectory in the proper direction, which helps to avoid negative metabolic programming effects. Protein intake during infancy and early childhood is of great importance, as it plays a key role in infant metabolic programming and the future risk of obesity. Breastfeeding provides the best nutrition in early life, with many benefits tailored for the baby, including the appropriate quantity and quality of proteins. Considering the high prevalence of childhood, and subsequent adult, obesity in the region, a virtual Middle East expert consensus meeting was held to discuss an effective approach for managing childhood obesity. Leading pediatric experts from Bahrain, Egypt, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates participated in the meeting. The experts discussed, debated, and agreed on certain directions, including the importance of educating parents, endorsing breastfeeding, and ensuring optimum quantity and quality intake of proteins in early life. This expert consensus may serve as the starting point for healthcare professionals in the region who are interested in shaping a healthy future for the generations to come.

**Keywords:** Pediatric obesity; Malnutrition; Non-communicable diseases; Middle East; Infant formula; Proteins; Milk, human

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CASE REPORT
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# Case Report: Hepatic Adenomatosis in a Patient With Prader–Willi Syndrome

*Hajar Dauleh*[1], *Ali Soliman*[1], *Basma Haris*[1], *Amal Khalifa*[1], *Noor Al Khori*[2] *and Khalid Hussain*[1]*

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Prader–Willi syndrome (PWS) is a genetic disorder caused by the lack of expression of genes on the paternally inherited chromosome region 15q11.2-q13. It is a multisystem disorder that is characterized by severe hypotonia with poor suck and feeding difficulties in early infancy, followed in early childhood by excessive eating and gradual development of morbid obesity. The incidence of type 2 diabetes mellitus is high, particularly in obese patients. Non-alcoholic fatty liver disease has also been reported in some patients with PWS. Liver adenomatosis is a benign vascular lesion of the liver, defined by the presence of >10 adenomas, in the otherwise healthy liver parenchyma. We report the first case of a patient with PWS with severe obesity, type 2 diabetes mellitus, and non-alcoholic fatty liver who also developed liver adenomatosis, review the pediatric literature on liver adenomatosis, and discuss the potential underlying mechanisms.

**Keywords: hepatic adenomatosis, Prader Willi syndrom, liver adenoma, oral contraception pills, Glycogen Storage Disease**

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## INTRODUCTION

Prader–Willi syndrome (PWS) is a complex multisystem disorder caused by lack of expression of genes on the paternally inherited chromosome region 15q11.2-q13. In the neonatal period, there is severe hypotonia with poor suck and feeding difficulties followed in infancy or early childhood by excessive eating and gradual development of morbid obesity. The syndrome is considered the most common genetic cause of obesity, occurring in 1:10,000–1:30,000 live births (1). Obesity and its related complications are the most common causes of morbidity and mortality in PWS. The mechanisms underlying the obesity include alterations in hypothalamic pathways that regulate satiety thus resulting in hyperphagia, disruption in hormones regulating appetite and satiety, and reduced energy expenditure (1).

Severe obesity is a strong risk factor for the development of type 2 diabetes mellitus (T2DM) in patients with PWS. T2DM in PWS occurs mostly in adults, but it has also been reported in patients under the age of 18 years (1). The prevalence of metabolic syndrome in obese patients with PWS

BMC Endocrine Disorders

RESEARCH Open Access

# Glycemic outcomes of Advanced Hybrid Closed Loop system in children and adolescents with Type 1 Diabetes, previously treated with Multiple Daily Injections (MiniMed 780G system in T1D individuals, previously treated with MDI)

Goran Petrovski*, Fawziya Al Khalaf, Judith Campbell, Emma Day, Douha Almajaly, Khalid Hussain, Maheen Pasha, Fareeda Umer, Manar Hamdan and Amel Khalifa

## Abstract

**Background:** The objective of this study was to evaluate the glycemic outcomes in children and adolescents with Type 1 Diabetes (T1D) previously treated with Multiple Daily Injections (MDI) using a structured initiation protocol for the Advanced Hybrid Closed Loop (AHCL) Minimed 780G insulin pump system.

**Methods:** In this prospective open label single-arm, single-center, clinical investigation, we recruited children and adolescents (aged 7–17 years) with T1D on MDI therapy and HbA1c below 12.5%. All participants followed a 10-day structured initiation protocol which included 4 steps: step 1: AHCL system assessment; step 2: AHCL system training; step 3: Sensor augmented pump therapy (SAP) for 3 days; step 4: AHCL system use for 12 weeks, successfully completing the training from MDI to AHCL in 10 days. The primary outcome of the study was the change in the time spent in the target in range (TIR) of 70–180 mg/dl and HbA1c from baseline (MDI + CGM, 1 week) to study phase (AHCL, 12 weeks). The paired student t-test was used for statistical analysis and a value $< 0.05$ was considered statistically significant.

**Results:** Thirty-four participants were recruited and all completed the 12 weeks study. TIR increased from $42.1 \pm 18.7\%$ at baseline to $78.8 \pm 6.1\%$ in the study phase ($p < 0.001$). HbA1c decreased from $8.6 \pm 1.7\%$ ($70 \pm 18.6$ mmol/mol) at baseline, to $6.5 \pm 0.7\%$ ($48 \pm 7.7$ mmol/mol) at the end of the study ($p = 0.001$). No episodes of severe hypoglycemia or DKA were reported.

**Conclusion:** Children and adolescents with T1D on MDI therapy who initiated the AHCL system following a 10-days structured protocol achieved the internationally recommended goals of glycemic control with TIR > 70% and a HbA1c of < 7%.

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[Intervention Review]

# Probiotics for treatment of chronic constipation in children

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## ABSTRACT

### Background

Functional constipation is defined as chronic constipation with no identifiable underlying cause. It is a significant cause of morbidity in children, accounting for up to 25% of visits to paediatric gastroenterologists. Probiotic preparations may sufficiently alter the gut microbiome and promote normal gut physiology in a way that helps relieve functional constipation. Several studies have sought to address this hypothesis, as well as the role of probiotics in other functional gut disorders. Therefore, it is important to have a focused review to assess the evidence to date.

### Objectives

To evaluate the efficacy and safety of probiotics for the management of chronic constipation without a physical explanation in children.

### Search methods

On 28 June 2021, we searched CENTRAL, MEDLINE, Embase, CINAHL, AMED, WHO ICTR, and ClinicalTrials.gov, with no language, date, publication status, or document type limitations.

### Selection criteria

We included randomised controlled trials (RCTs) that assessed probiotic preparations (including synbiotics) compared to placebo, no treatment or any other interventional preparation in people aged between 0 and 18 years old with a diagnosis of functional constipation according to consensus criteria (such as Rome IV).

### Data collection and analysis

We used standard methodological procedures expected by Cochrane.

### Main results

We included 14 studies (1127 randomised participants): 12 studies assessed probiotics in the treatment of functional constipation, whilst two studies investigated synbiotic preparations.

Three studies compared probiotics to placebo in relation to the frequency of defecation at study end, but we did not pool them as there was very significant unexplained heterogeneity. Four studies compared probiotics to placebo in relation to treatment success. There may be no difference in global improvement/treatment success (RR 1.29, 95% CI 0.73 to 2.26; 313 participants; low-certainty evidence). Five

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# Social distance and stigma towards persons with serious mental illness among medical students in five European Central Asia countries

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ABSTRACT

The study investigated behavioral measures of social distance (i.e., desired proximity between self and others in social contexts) as an index of stigma against those with mental illness among medical students in the Republic of North Macedonia, Turkey, Azerbaijan, Kazakhstan, and Poland, using the Reported and Intended Behavior Scale (RIBS), a standardized, self-administered behavioral measure based on the Star Social Distance Scale. The students' responses to standardized clinical vignettes on schizophrenia, and depression with suicidal ideation, were also assessed. A total of 257 North Macedonian (females, 31.5%; 1–4 grades, 189; 5–6 grades, 68); 268 Turkish (females, 43.3%; 1–4 grades, 90; 5–6 grades, 178); 450 Kazakh (females, 28.4%, 71.6%; 1–4 grades, 312; 5–6 grades, 138); 512 Azerbaijani (females, 24%; 1–4 grades, 468; 5–6 grades, 44; females, 24%), and 317 Polish (females, 59.0%; 1–4 grades, 208; 5–6 grades, 109) students were surveyed. The responses on the RIBS social distance behavior measures did not improve with advancing medical school grade, but students across all sites viewed schizophrenia and depression as real medical illnesses. The results support the development of enhanced range of integrated training opportunities for medical student to socially interact with persons with mental illness sharing their experiences with them.

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**Original Article: Clinical Investigation**

# Plate Objective Scoring Tool: A new preoperative indicator of penile curvature degree in children with distal hypospadias

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**Abbreviations & Acronyms**
IQR = interquartile range
POST = Plate Objective Scoring Tool
ROC = receiver operating characteristic
VC = ventral curvature

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**Objectives:** There is an unmet need for preoperative methods that surgeons can use to objectively quantify hypospadias anatomic variables and determine risk of penile curvature. We, therefore, assessed whether Plate Objective Scoring Tool measurements were correlated with degree of ventral curvature in affected children.

**Methods:** Patients undergoing distal hypospadias repair were enrolled into the study between January 2018 and December 2020 and were categorized independently by at least two surgeons using Plate Objective Scoring Tool. Scores were compared statistically to determine the degree of ventral curvature and requirement for correction.

**Results:** Sixty-five patients with a median age of 18 months (interquartile range 13–26) were enrolled into the study prior to surgery for primary distal hypospadias. Patient probability of significant postoperative curvature (>20°) was determined with moderate confidence using a cutoff Plate Objective Scoring Tool score of 1 (sensitivity 75%, specificity 60%). Presurgery Plate Objective Scoring Tool scores were negatively correlated with subsequent degree of curvature ($r = -0.37$, $P = 0.003$), with values <1.0 predicting >20° curvature.

**Conclusions:** Plate Objective Scoring Tool scoring offers a succinct method of describing hypospadias severity and correlates well with postoperative outcomes. The Plate Objective Scoring Tool system can therefore be used to objectively predict the likelihood of penile curvature and aid communication between surgeons and researchers, as well as improving parental counseling.

**Key words:** children, chordee, hypoplasia, hypospadias, prognostic, score.

## Introduction

Hypospadias is one of the most common male genital malformations and includes a broad spectrum of phenotypic presentations. Some hypospadias cases are mild with minor cosmetic impact, whereas others display significant deformities with long-term functional, psychological, and fertility consequences.[1] As such, there is a clear need for standardized, reproducible, and sensitive methods of comparing key variables that allow researchers to communicate effectively, as well as informing objective preoperative parental counseling.

The most frequently used approach for hypospadias classification is meatal position, but this is just one of several factors influencing the extent of malformation and resulting postoperative outcomes.[2] Other essential variables with meaningful impact include urethral plate quality,[3] degree of ventral chordee,[4] and glans size.[5] Significant efforts have, therefore, been made to incorporate these factors via introduction of the GMS score, which considers observable glans size (G), meatal position (M), and overall curvature (S). However, this scale uses only subjective assessment of the (G) and (M) components, as well as limited sensitivity for determining curvature (S), which can only be assessed intraoperatively.

Penile VC occurs at higher frequency in more severe forms of hypospadias, with several possible causes including skin tethering, fibrous bands within the perispongiosal territory, and ventrodorsal corporeal disproportion. Although crude impressions of penile curvature can be obtained from patient history and bedside physical examination, the true extent of malformation and the need for surgical repair can only be determined intraoperatively. Although penile curvature occurs less frequently in distal hypospadias, it is still essential to detect even minor

Histopathology

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# Renal cell carcinoma in children and adolescents: a retrospective study of a French–Italian series of 93 cases

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**Renal cell carcinoma in children and adolescents: a retrospective study of a French–Italian series of 93 cases**

*Aims*: Renal cell carcinomas (RCCs) represent 2–5% of kidney malignancies in children and adolescents. Appropriate diagnostic and classification are crucial for the correct management of the patients and in order to avoid inappropriate pre-operative chemotherapy, which is usually recommended if a Wilms' tumour is suspected.

*Methods and results*: A French–Italian series of 93 renal cell carcinomas collected from 1990 to 2019 in patients aged less than 18 years was reclassified according to the 2016 World Health Organization (WHO) classification and the latest literature. *TFE3* and *TFEB* fluorescence *in-situ* hybridisation (FISH) analyses and a panel of immunohistochemical stains were applied. The median age at diagnosis was 11 years (range = 9 months–17 years). *MiT* family (*MiTF*) translocation RCCs accounted for 52% of the tumours, followed by papillary (20%) and unclassified RCCs (13%). Other subtypes, such as SDHB-deficient and fumarate hydratase-deficient RCCs, represented 1–3% of the cases. We also described a case of *ALK*-rearranged RCC with a metanephric adenoma-like morphology.

*Conclusion*: A precise histological diagnosis is mandatory, as targeted therapy could be applied for some RCC subtypes, i.e. *MiTF*-translocation and *ALK*-translocation RCC. Moreover, some RCC subtypes may be associated with a predisposition syndrome that

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Original Research

# Treatment of patients with stage I focal anaplastic and diffuse anaplastic Wilms tumour: A report from the SIOP-WT-2001 GPOH and UK-CCLG studies

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**KEYWORDS**
Wilms tumour;
Anaplasia;
Stage I;
Focal and diffuse;
Outcomes

**Abstract** ***Background:*** Anaplasia is an unfavourable prognostic histological feature in Wilms tumour (WT). Patients with stage I anaplastic WT (AWT) typically achieve good outcomes, albeit with more treatment than for stage I non-AWT. Since the SIOP-WT-2001 study, patients with focal AWT (FAWT) have been classified as intermediate risk and received less intense treatment than patients with diffuse AWT (DAWT). The aim of the study was to analyse outcomes in these patients.

***Patients and methods:*** This was a retrospective analysis of clinicopathological features and outcomes of 59 patients with stage I AWT (19 FAWT, 40 DAWT) from the SIOP-WT-2001 GPOH and UK-CCLG groups. The patients with FAWT were treated as intermediate-risk WT, with 8 weeks of vincristine and actinomycin D (4 weeks pre-operatively, and 4 weeks post-operatively). For comparison, we also assessed outcomes in 818 patients with stage I intermediate-risk non-AWT (IR-non-AWT). The patients with DAWT were treated with vincristine, actinomycin D and doxorubicin for 31 weeks. No group received radiotherapy.

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# The efficacy of non-fasting ketogenic diet protocol in the management of intractable epilepsy in pediatric patients: a single center study from Saudi Arabia

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**Abstract**

**Objective:** To review the characteristics and outcomes of pediatric patients on a ketogenic diet (KD), an established treatment option for individuals with intractable epilepsy, in a tertiary epilepsy center.

**Methods:** This retrospective study included pediatric patients diagnosed with intractable epilepsy who had experienced no benefits from at least two appropriately chosen antiseizure medications. All patients were hospitalized, started a KD without fasting, and were observed for complications and tolerance. The etiology of epilepsy, side effects, and KD efficacy on seizure outcomes were also examined.

**Results:** Of 16 children included in the study, nine (56%) experienced significant seizure improvement, with three becoming seizure-free during the KD. Ten patients were fed orally, and six were fed through gastrostomy feeding tubes. Most were on a 3:1 ratio, and nine reached ketosis within the first three days of KD initiation. Initial recurrent hypoglycemia was documented in four patients, and four experienced vomiting and acidosis. Most families complied with the diet, and all of the children gained weight during the study period.

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ORIGINAL ARTICLE

# Effect of mRNA Vaccine Boosters against SARS-CoV-2 Omicron Infection in Qatar

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## ABSTRACT

### BACKGROUND

Waning of vaccine protection against coronavirus disease 2019 (Covid-19) and the emergence of the omicron (or B.1.1.529) variant of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have led to expedited efforts to scale up booster vaccination. Protection conferred by booster doses of the BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna) vaccines in Qatar, as compared with protection conferred by the two-dose primary series, is unclear.

### METHODS

We conducted two matched retrospective cohort studies to assess the effectiveness of booster vaccination, as compared with that of a two-dose primary series alone, against symptomatic SARS-CoV-2 infection and Covid-19–related hospitalization and death during a large wave of omicron infections from December 19, 2021, through January 26, 2022. The association of booster status with infection was estimated with the use of Cox proportional-hazards regression models.

### RESULTS

In a population of 2,239,193 persons who had received at least two doses of BNT162b2 or mRNA-1273 vaccine, those who had also received a booster were matched with persons who had not received a booster. Among the BNT162b2-vaccinated persons, the cumulative incidence of symptomatic omicron infection was 2.4% (95% confidence interval [CI], 2.3 to 2.5) in the booster cohort and 4.5% (95% CI, 4.3 to 4.6) in the nonbooster cohort after 35 days of follow-up. Booster effectiveness against symptomatic omicron infection, as compared with that of the primary series, was 49.4% (95% CI, 47.1 to 51.6). Booster effectiveness against Covid-19–related hospitalization and death due to omicron infection, as compared with the primary series, was 76.5% (95% CI, 55.9 to 87.5). BNT162b2 booster effectiveness against symptomatic infection with the delta (or B.1.617.2) variant, as compared with the primary series, was 86.1% (95% CI, 67.3 to 94.1). Among the mRNA-1273–vaccinated persons, the cumulative incidence of symptomatic omicron infection was 1.0% (95% CI, 0.9 to 1.2) in the booster cohort and 1.9% (95% CI, 1.8 to 2.1) in the nonbooster cohort after 35 days; booster effectiveness against symptomatic omicron infection, as compared with the primary series, was 47.3% (95% CI, 40.7 to 53.3). Few severe Covid-19 cases were noted in the mRNA-1273–vaccinated cohorts.

### CONCLUSIONS

The messenger RNA (mRNA) boosters were highly effective against symptomatic delta infection, but they were less effective against symptomatic omicron infection. However, with both variants, mRNA boosters led to strong protection against Covid-19–related hospitalization and death. (Funded by Weill Cornell Medicine–Qatar and others.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Abu-Raddad can be contacted at lja2002@qatar-med.cornell.edu or at the Infectious Disease Epidemiology Group, World Health Organization Collaborating Center for Disease Epidemiology Analytics on HIV/AIDS, Sexually Transmitted Infections, and Viral Hepatitis, Weill Cornell Medicine–Qatar, Qatar Foundation–Education City, P.O. Box 24144, Doha, Qatar.

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RESEARCH PAPER

# Scapular Fractures at a Level 1 Trauma Center: A Cross-Sectional Study

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## ABSTRACT

Purpose: Scapular fractures are uncommon injuries that account for up to 1% of all fractures and 5% of all shoulder girdle fractures. Moreover, most of the evidence on the treatment of scapular fractures stems from case series, with paucity of comparative studies. Despite the lack of standardized criteria for the operative treatment of scapular fractures, a set of suggested radiological parameters has been recently reported. The primary aim of this study was to compare the treatment implemented for scapular fractures in comparison with standard published criteria. The secondary aim was to investigate epidemiological parameters of scapular fractures at a level 1 trauma center.

Methods: In this cross-sectional study of scapular fractures at a level 1 trauma center, data were collected between December 2012 and January 2016. Data of all scapular fractures that presented to our center were retrospectively collected through electronic medical records. Identified cases of scapular fractures were then evaluated whether surgical treatment was indicated in accordance with recent standard operative criteria. Percentages were used to express the number of cases that were operatively indicated according to the predefined criteria and the number of cases operatively treated at our institution.

Results: A total of 52 patients met the inclusion criteria of having scapular fractures documented on radiography and Computed tomography (CT). The mean age of the patients was 38.5 years, with the majority being men (92.3%). The most common mechanism of injury was a fall from a considerable height in 26% of the cases. Of the included patients, 53.8% were polytraumatized, and the most frequent concomitant traumatic injury was rib fractures (26.9%). Only 33% of intra-articular glenoid fractures

Histopathology

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REVIEW

# Pathology of Wilms' tumour in International Society of Paediatric Oncology (SIOP) and Children's oncology group (COG) renal tumour studies: Similarities and differences

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**Pathology of Wilms' tumour in International Society of Paediatric Oncology (SIOP) and Children's oncology group (COG) renal tumour studies: Similarities and differences**

Excellent outcomes for patients with Wilms' tumour (WT), >90% for all stages together, have been achieved through researching WT in multicentre and multinational trials and studies in the last 50 years, led by two major groups—the International Society of Paediatric Oncology (SIOP) and the Children's Oncology Group (COG) (previously the National Wilms' Tumour Study Group). Despite the two groups having different approaches, the survival outcomes are remarkably similar. In general, in the SIOP approach, which is followed in Europe and most other countries around the world, patients are first treated with preoperative chemotherapy; this is followed by surgery and, if necessary, postoperative chemotherapy and radiotherapy. In the COG approach, which is mainly followed in North America, patients are treated with upfront surgery, followed, if necessary, by postoperative chemotherapy and radiotherapy. In both groups, postoperative treatment primarily depends on tumour histological classification and stage, although, in recent studies, other prognostic factors have also been included (tumour volume, response to preoperative chemotherapy, and molecular markers). Owing to separate initial treatments, there are differences in histological assessment and subtyping of WT, and, more importantly, in staging criteria. In this review, we discuss the similarities and differences between the two groups in order to help pathologists who are dealing with WT to understand and follow the pathological protocol that is appropriate for a particular case, because, in many centres, both approaches may be followed, depending on individual case/patient circumstances.

Keywords: COG, SIOP, staging criteria, subclassifications, Wilms' tumour

## Introduction

Wilms' tumour (WT) or nephroblastoma is the most common primary renal tumour of childhood, accounting for ~85% of primary renal tumours in this age group, with a median age of 3.4 years at diagnosis.[1,2] The outcome of patients with WT has improved over time, with a population-based 5-year

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BMJ Open Respiratory Research

# Treatment patterns and frequency of key outcomes in acute severe asthma in children: a Paediatric Research in Emergency Departments International Collaborative (PREDICT) multicentre cohort study

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## ABSTRACT

**Rationale** Severe acute paediatric asthma may require treatment escalation beyond systemic corticosteroids, inhaled bronchodilators and low-flow oxygen. Current large asthma datasets report parenteral therapy only.

**Objectives** To identify the use and type of escalation of treatment in children presenting to hospital with acute severe asthma.

**Methods** Retrospective cohort study of children with an emergency department diagnosis of asthma or wheeze at 18 Australian and New Zealand hospitals. The main outcomes were use and type of escalation treatment (defined as any of intensive care unit admission, nebulised magnesium, respiratory support or parenteral bronchodilator treatment) and hospital length of stay (LOS).

**Measurements and main results** Of 14 029 children (median age 3 (IQR 1–3) years; 62.9% male), 1020 (7.3%, 95% CI 6.9% to 7.7%) had treatment escalation. Children with treatment escalation had a longer LOS (44.2 hours, IQR 27.3–63.2 hours) than children without escalation 6.7 hours, IQR 3.5–16.3 hours; p<0.001). The most common treatment escalations were respiratory support alone (400; 2.9%, 95% CI 2.6% to 3.1%), parenteral bronchodilator treatment alone (380; 2.7%, 95% CI 2.5% to 3.0%) and both respiratory support and parenteral bronchodilator treatment (209; 1.5%, 95% CI 1.3% to 1.7%). Respiratory support was predominantly nasal high-flow therapy (99.0%). The most common intravenous medication regimens were: magnesium alone (50.4%), magnesium and aminophylline (24.6%) and magnesium and salbutamol (10.0%).

**Conclusions** Overall, 7.3% children with acute severe asthma received some form of escalated treatment, with 4.2% receiving parenteral bronchodilators

## Key messages

### What is already known on this topic

- Some children with acute asthma exacerbations require escalation of care beyond inhaled bronchodilators and oral corticosteroids; however, rates of intravenous therapy vary between 3.4% (in the UK and Ireland) to 10.5% in the USA.
- To date, no large dataset has reported on both intravenous and respiratory support following first-line management for children presenting acutely to hospital with asthma.

### What this study adds

- This study of 14 029 New Zealand and Australian children presenting to hospital with acute wheeze or asthma demonstrates wide variation in management: 7.3% received some form of escalated treatment with 4.2% receiving parenteral bronchodilators and 4.3% respiratory support.
- Severe outcomes were rare, with 243 children admitted to intensive care; 22 received non-invasive ventilation and only 4 were intubated.

### How this study might affect research, practice or policy

- Although large multicentre studies are required to guide future treatment, significant clinical events such as intubation, and/or use of non-invasive ventilation are too rare to be suitable for use as outcome measures in future randomised clinical trials.

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BRIEF REPORT

# Importance of establishing antibody specificity in multisystem inflammatory syndrome in newborn during the COVID-19 pandemic

Multisystem inflammatory syndrome in newborns (MIS-N) has increasingly been reported in patients with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1,2] MIS-N can be secondary to immune-mediated injuries, due to transplacental maternal or neonatal antibodies produced during the infection. This process is similar to multisystem inflammatory syndrome in children.[3] Transplacental transfer of maternal SARS-CoV-2 immunoglobulin G (IgG) antibodies can be protective,[4] but sometimes in-utero transfer of these antibodies, concomitant other inflammatory cytokines, may trigger MIS-N. Increased viral transmission and mass vaccination have increased SARS-CoV-2 seroprevalence, and babies are increasingly being born with positive antibodies.[5] We describe a baby with multi-organ dysfunction, due to placental abruption, but confounded by SARS-CoV-2 antibodies consistent with MIS-N. Parental consent was provided.

A male baby weighing 2,690 kg was born at 33 + 5 weeks to a primipara mother with placenta previa. She was an unvaccinated nurse, with potential exposure to SAR-CoV-2, who tested negative before labour. The baby was born vigorous, but pale, and required intubation at 11 min. His cord gas was normal, but he had low haemoglobin (11 g/L). The initial treatment included mechanical ventilation, empirical antibiotics, fluid management, packed red blood cells (PRBC) and fresh frozen plasma (FFP) transfusions for abnormal coagulation. His renal function started to deteriorate 12 h after transfusion, with no urine output since birth and increasing hyperkalaemia. At 24 h, he was transferred to our quaternary hospital, in case he needed peritoneal dialysis. He presented with severe multi-organ dysfunction, with respiratory distress needing ventilation and cardiac compromise with low blood pressure. An echocardiogram suggested mild left ventricular dysfunction and exponential elevation of cardiac biomarkers, N-terminal-pro-B-type natriuretic peptide (>70,000 pg/ml) and troponin-T (2,046 ng/ml), suggesting myocardial injury. He had acute renal failure, with elevated serum potassium (9.5 mmol/L) and rising urea and creatinine and needed peritoneal dialysis from 3 to 11 weeks of life. Gastric bleeding, with abnormal clotting and platelet levels, required multiple vitamin K doses, PRBC, cryoprecipitate, FFP and platelet transfusions. His liver enzymes were significantly elevated on admission, but gradually declined, with extensive necrosis visible on his abdominal ultrasound.

The baby was not encephalopathic, with a discontinuous background on amplitude-integrated electroencephalogram and normal cerebral near-infrared spectroscopy. Brain magnetic resonance imaging on day 19 showed minor multifocal deep white matter abnormalities.

All his inflammatory markers were markedly elevated: Serum ferritin (3,825 mcg/L), lactate dehydrogenase (>1,200 IU/L), procalcitonin (7.21 ng/ml) and D-Dimer concentration (>7,500).

Multiple nasopharyngeal swabs, tracheal aspirate and stool samples tested negative for SARS-CoV-2, and he and his mother were negative for SARS-CoV-2 immunoglobulin M antibodies. However, he tested positive for immunoglobulin G (IgG) antibodies against SARS-CoV-2 with titres of 210 and 155 BAU/ml on days 3 and 11 of life. His mother's level was 17.9 BAU/ml.

We suspected MIS-N, as SARS-CoV-2 IgG was present, and he received immunomodulatory therapy from day 2 of life, with a single dose of intravenous immunoglobulin (1 g/kg) and daily methylprednisolone (1 mg/kg). Enzyme-linked immunosorbent assays showed that he and his mother had antibodies against the SARS-CoV-2 spike protein, but not nucleoprotein. MIS-N was thus ruled out, and immunomodulator therapy discontinued. The baby was extubated at 3 weeks of life, but his liver failure continued. His clinical condition progressively worsened, and he died 93 days after birth.

The patient's severe multi-organ dysfunction was related to placental abruption, but the degree of bleeding was unclear at birth. High levels of inflammatory markers, cardiac biomarkers and mild left ventricular dysfunction on admission, during the pandemic, suggested MIS-N. He tested negative for the virus, but his mother was positive for SARS-CoV-2 IgG antibodies and his antibodies were 6 times her levels. The initial immunomodulatory treatment, due to suspected MIS-N, was stopped after we established the antigen specificity of the antibodies. The results were inconsistent with natural infection, and vaccination-derived antibodies from transfusions were suspected. The mother's serum

**Abbreviations:** IgG, immunoglobulin G; MIS-N, multisystem inflammatory syndrome in newborns; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

frontiers in Physiology

ORIGINAL RESEARCH
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# Hemodynamic and Structural Comparison of Human Fetal Heart Development Between Normally Growing and Hypoplastic Left Heart Syndrome-Diagnosed Hearts

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Congenital heart defects (CHDs) affect a wide range of societies with an incidence rate of 1.0–1.2%. These defects initiate at the early developmental stage and result in critical health disorders. Although genetic factors play a role in the formation of CHDs, the occurrence of cases in families with no history of CHDs suggests that mechanobiological forces may also play a role in the initiation and progression of CHDs. Hypoplastic left heart syndrome (HLHS) is a critical CHD, which is responsible for 25–40% of all prenatal cardiac deaths. The comparison of healthy and HLHS hearts helps in understanding the main hemodynamic differences related to HLHS. Echocardiography is the most common imaging modality utilized for fetal cardiac assessment. In this study, we utilized echocardiographic images to compare healthy and HLHS human fetal hearts for determining the differences in terms of heart chamber dimensions, valvular flow rates, and hemodynamics. The cross-sectional areas of chamber dimensions are determined from 2D b-mode ultrasound images. Valvular flow rates are measured via Doppler echocardiography, and hemodynamic quantifications are performed with the use of computational fluid dynamics (CFD) simulations. The obtained results indicate that cross-sectional areas of the left and right sides of the heart are similar for healthy fetuses during gestational development. The left side of HLHS heart is underdeveloped, and as a result, the hemodynamic parameters such as flow velocity, pressure, and wall shear stress (WSS) are significantly altered compared to those of healthy hearts.

**Keywords: congenital heart defects, fetal heart development, hypoplastic left heart syndrome, computational fluid dynamics, tricuspid valve, mitral valve, disturbed hemodynamics, echocardiography**

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# Moral Distress in Healthcare Providers Who Take Care of Critical Pediatric Patients throughout Italy—Cultural Adaptation and Validation of the Italian Pediatric Instrument

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**Abstract:** Background: Although Moral Distress (MD) is a matter of concern within the Pediatric Intensive Care Unit (PICU), there is no validated Italian instrument for measuring the phenomenon in nurses and physicians who care for pediatric patients in Intensive Care. The authors of the Italian Moral Distress Scale-Revised (Italian MDS-R), validated for the adult setting, in 2017, invited further research to evaluate the generalizability of the scale to clinicians working in other fields. Our study aims to reduce this knowledge gap by developing and validating the pediatric version of the Italian MDS-R. Methods: We evaluated the new instrument for construct validity, then we administered it in a multicenter, web-based survey that involved healthcare providers of three PICUs and three adult ICUs admitting children in northern, central, and southern Italy. Finally, we tested it for internal consistency, confirmatory factorial validity, convergent validity, and differences between groups analysis. Results: The 14-item, three-factor model best fit the data. The scale showed good reliability (a = 0.87). Still, it did not correlate with the Emotional Exhaustion and Depersonalization sub-scales of the Maslach Burnout Inventory (MBI) or with the 2-item Connor-Davidson Resilience Scale (CD-RISC 2) or the Satisfaction with Life Scale (SWLS). A mild correlation was found between the *Italian Pediatric MDS-R* score and intention to resign from the job. No correlation was found between MD and years of experience. Females, nurses, and clinicians who cared for COVID-19 patients had a higher MD score. Conclusions: The *Italian Pediatric MDS-R* is a valid and reliable instrument for measuring MD among Italian health workers who care for critically ill children. Further research

Review Article

# Diagnosis and Therapeutic Cardiac Catheterization of Symptomatic Bicuspid Aortic Stenosis in the Pediatric Population

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## ABSTRACT

Bicuspid aortic valve (BAV) is the most common congenital heart disease with a prevalence of 0.5%-1.3% of the population. Many children with BAV are asymptomatic. Clinically relevant abnormal valve function usually occurs in adulthood. However, in rare cases, children can fail to thrive which requires valvular intervention. In this review, we will explore in more detail the anatomy of the BAV, clinical presentation of BAV, diagnosis of BAV, and its function by echocardiography, and indications for transcatheter intervention in the pediatric population.

**Key words:** Anatomy, aortic stenosis, aortopathy, balloon valvuloplasty, bicuspid aortic valve, morphology

## INTRODUCTION

Bicuspid aortic valve (BAV) is the most common congenital heart disease with a prevalence of up to 1.3%. It is more common in males than females with a ratio of 2.65:1.[1] Studies found a heritable component to BAV disease, a first-degree relative of patients with BAV has a high chance (up to 10%) of having BAV. Hence, screening echocardiogram for first-degree relatives is recommended.[2]

The fetal heart is developed by 8 weeks of gestation. The semilunar valves are developed by the division of the truncus arteriosus into two separate channels that eventually form the aortic and pulmonary trunks. A small swelling appears on the inferior margins of each trunk, forming the basis of the valve leaflets. The BAV is believed to be due to a fusion of the aortic cusps during valvulogenesis.[3] In this review, we will explore in more detail the anatomy of the BAV, clinical presentation, echocardiography, and indications for transcatheter intervention.

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## ANATOMY

Normally, the aortic valve includes three cusps: right, left, and noncoronary cusps. In BAV, there are only two cusps and usually unequal in size. The inequality is due to the fusion of two cusps leading to one larger cusp with a presence of a central raphe or fibrous ridge.[4]

## TYPES OF BICUSPID AORTIC VALVE

There are multiple published classifications of BAV. Below is the classification from the International BAV Consortium [Figure 1]:

1. Type 1: Fusion of the right and left coronary cusps
2. Type 2: Fusion of the right and noncoronary cusps
3. Type 3: Fusion of the left and noncoronary cusps.



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# Myths, misconceptions, and hesitancy in people residing in Qatar toward mRNA COVID-19 vaccines: An experience exchange from Qatar University health center

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## ABSTRACT

The hesitancy in taking COVID-19 vaccines is a complex process influenced by several factors, including individual, social, and cultural. Health literacy and community awareness around mRNA COVID-19 vaccines are critical for successfully combating the pandemic. Healthcare professionals, including family physicians and nurses, can help increase community awareness and mitigate some misconceptions and hesitancy regarding mRNA COVID-19 vaccines in people's attitudes. Therefore, in this study, we aimed to explore how the interaction between an individual's social identities such as gender, ethnicity, culture, knowledge, and belief impact their hesitancy and attitudes toward mRNA COVID-19 vaccines.

We aimed to describe our experience in dealing with people residing in Qatar from the perspective of healthcare practitioners from the Qatar University Health Center during the period when mRNA COVID-19 vaccines was introduced in a time frame of 6 months (April to October, 2021).

We identified several factors associated with the reluctance to receive mRNA COVID-19 vaccines once vaccination services were available, affordable, and accessible to everyone in Qatar (Table 1). Most individuals were hesitant and refused to take mRNA COVID-19 vaccines owing to the unjustified myths and fear about potential side effects of vaccines in general and unknown long-term effects of vaccination, especially among women who were uneducated. We believe we have been able to put forth a fair, unbiased, and balanced argument between an individual's right to take or refuse the vaccine and the

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RESEARCH ARTICLE

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# Persistence of an epidemic cluster of *Rhodotorula mucilaginosa* in multiple geographic regions in China and the emergence of a 5-flucytosine resistant clone

Jing-Jing Huang[a,b,c], Xin-Fei Chen[a,b,c], Clement K.M. Tsui[d,e,f†], Chong-Jie Pang[g], Zhi-Dong Hu[h], Yi Shi[i], Wei-Ping Wang[j], Lan-Ying Cui[k], Yu-Ling Xiao[l], Jie Gong[m], Xin Fan[n], Ying-Xing Li[c,o], Ge Zhang[a,c], Meng Xiao[a,c] and Ying-Chun Xu[a,c]

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**ABSTRACT**

*Rhodotorula mucilaginosa*, an environmental yeast widely used in industry and agriculture, is also an opportunistic pathogen resistant to multi-antifungals. During the national surveillance in China, *R. mucilaginosa* has been documented from various hospitals and regions. At present, the molecular epidemiology of invasive infections caused by *R. mucilaginosa* and their resistance profiles to antifungals were unknown. Here we collected 49 strains from four hospitals located in different geographic regions from 2009 to 2019 in China, determined their genotypes using different molecular markers and quantified susceptibilities to various antifungals. Sequencing of ITS and D1/D2 regions in rDNA indicated that 73.5% (36/49) of clinical strains belong to same sequence type (rDNA type 2). Microsatellite (MT) genotyping with 15 (recently developed) tandem repeat loci identified 5 epidemic MT types, which accounted for 44.9% (22/49) of clinical strains, as well as 27 sporadic MT types. Microsatellite data indicated that the presence of an epidemic cluster including 35 strains (71.4%) repeatedly isolated in four hospitals for eight years. Single nucleotide variants (SNVs) from the whole genome sequence data also supported the clustering of these epidemic strains due to low pairwise distance. In addition, phylogenetic analysis of SNVs from these clinical strains, together with environmental and animal strains showed that the closely related epidemic cluster strains may be opportunistic, zoonotic pathogens. Also, molecular data indicated a possible clonal transmission of pan echinocandins-azoles-5-flucytosine resistant *R. mucilaginosa* strains in hospital H01. Our study demonstrated that *R. mucilaginosa* is a multi-drug resistant pathogen with the ability to cause nosocomial infection.

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**KEYWORDS** *Rhodotorula mucilaginosa*; molecular typing; WGS; genomic epidemiology; outbreak, zoonotic

## Introduction

Invasive fungal diseases (IFD) are associated with high mortality and morbidity [1]. In the last two decades, reports of invasive infections caused by *Rhodotorula mucilaginosa* have increased [2]. Although *R. mucilaginosa* is an environmental yeast occurring in the soil, lakes and deep-sea [3], it has emerged as an opportunistic pathogen in cases of fungemia, central nervous system infections, ocular infections, peritonitis and endocarditis with 9.1%–15% mortality [4,5]. In terms of antifungal susceptibility profiles,

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# The prevalence of asthma, allergic rhinitis, and eczema among school-aged children in Qatar: A Global Asthma Network Study

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## Abstract

This cross-sectional study aims to utilize the Global Asthma Network (GAN) questionnaires to estimate the prevalence of asthma, allergic rhinitis, and eczema among children in Qatar. The study population was comprised of children ages 6–7 and 13–14 years, along with their parents or guardians. The English and Arabic versions of the GAN questionnaires were used to collect data for this study. A total of 2646 participants were recruited (1210 in the 6–7 years age group and 1436 in the 13–14 years age group), in addition to a total of 3831 parents or guardians. The overall prevalence of diagnosed asthma, lifetime allergic rhinitis, and diagnosed eczema in our study sample were as follows: 34.6%, 30.9%, and 37.4%, respectively. The current study showed an increased prevalence rate of asthma and eczema comparing to previous local estimates. These rates were higher in some cases or comparable in other cases to those found elsewhere. It is recommended that future research focus on studying the various factors contributing to the cases of asthma, allergic rhinitis, and eczema in Qatar. The reporting of this study conforms with the STROBE statement.

**KEYWORDS**
allergic rhinitis, asthma, eczema, Global Asthma Network, prevalence, Qatar

## 1 | INTRODUCTION

Globally, asthma is considered a major public health challenge. Due to high morbidity and relatively low mortality,[1] and with current cases in excess of 300 million worldwide, the Global Asthma Network (GAN) declares it as a source of financial burden in both developed and developing nations.[2] Among children, asthma is the most common chronic disease, with a constant burden on healthcare systems due to rising prevalence rates, especially in low- and middle-income countries.[3] The International Study of Asthma and Allergies in Childhood (ISAAC) of 13–14 years adolescents ($n$ = 798,685) showed a wide variation in the prevalence of recent wheeze and severe asthma symptoms in the past 12 months across 97 countries.[2]

In the Middle East region, a wide range of prevalence rates have been reported ranging from 1% to 17% in North Africa and the East Mediterranean region. While the Asthma Insights and Reality in the

**Abbreviations:** AIRMAG, Asthma Insights and Reality in the Maghreb; GAN, Global Asthma Network; ISAAC, International Study of Asthma and Allergies in Childhood; SPSS, Statistical Package for Social Sciences; UAE, United Arab Emirates.

SURGICAL TECHNIQUE

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# Orchio-Septopexy: A new technique to cover and fix detorsed testis undergoing fasciotomy of tunica albuginea

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## ABSTRACT

*Purpose:* Compartment Syndrome (CS) has been recognized as a potential factor that worsens testicular viability after detorsion, especially in borderline cases of prolonged ischemia. Fasciotomy of the testicular tunica albuginea to relieve the pressure associated with CS has been proposed to accommodate edema after detorsion, embracing the raw fasciotomy area with tunica vaginalis flap (TVF) or graft. Fashioning the TVF can be tedious in cases of severe scrotal edema. Herein we present a technique that facilitates and expedites the procedure, maintaining the fasciotomy area decompressed.
*Materials and Methods:* In testicular torsion, where the testis remains with dark coloration and questionable viability after detorsion a longitudinal releasing incision is made in the tunica albuginea (fasciotomy) to decrease compartmental pressure. If signs of parenchymal recovery (bleeding points, better color) are seen an orchio-septopexy is performed, suturing the incised albuginea's edges to the septum with a running suture, avoiding CS as well as re-torsion.
*Results:* Orchio-septopexy was performed in 11 cases with a mean age of 11.9 years (3-17). All cases had clinic follow-up and testicular Doppler US with a mean of 9.5 months (6-24). 6/11 cases (54%) were salvaged, with good vascularity in the Doppler US and maintained more than 50% testicular volume compared to the contralateral side.
*Conclusion:* Orchio-septopexy after testicular fasciotomy is a simple and fast technique that can be utilized in cases of prolonged testicular ischemia and questionable viability. More than half of the testes recovered, encouraging us to propose its utilization as well as its validation by other surgeons.

## ARTICLE INFO

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## INTRODUCTION

Testicular torsion (TT) is a common emergency condition encountered by Pediatric urologist with annual incidence of 3.8 per 100,000 pediatric patients (1). The clinical management of TT is critical, relying on prompt assessment and surgical exploration (2). The testicle viability is time sensitive to ischemia, with rate of orchiectomy reaching 80- 90% when ischemia time exceeds 24 hours (3). Different methods were used aiming to improve the salvage rate of testis post torsion, namely: educational material for health care takers, initial care of TT

[Intervention Review]

# Tacrolimus (FK506) for induction of remission in corticosteroid-refractory ulcerative colitis

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## ABSTRACT

### Background

There are a limited number of treatment options for people with corticosteroid-refractory ulcerative colitis. Animal models of inflammatory bowel disease and uncontrolled studies in humans suggest that tacrolimus may be an effective treatment for ulcerative colitis.

### Objectives

To evaluate the efficacy and safety of tacrolimus for induction of remission in people with corticosteroid-refractory ulcerative colitis.

### Search methods

We searched the Cochrane Gut group specialised register, CENTRAL, MEDLINE (PubMed), Embase, Clinicaltrials.gov and WHO ICTRP from inception to October 2021 to identify relevant randomised controlled trials (RCT).

### Selection criteria

Two review authors independently selected potentially relevant studies to determine eligibility based on the prespecified criteria.

### Data collection and analysis

Two review authors independently extracted data and analysed them using Review Manager Web. The primary outcomes were induction of remission and clinical improvement, as defined by the studies and expressed as a percentage of the participants randomised (intention-to-treat analysis).

### Main results

This review included five RCTs with 347 participants who had active ulcerative colitis or ulcerative proctitis. The duration of intervention varied between two weeks and eight weeks.

### Tacrolimus versus placebo

Tacrolimus (oral and rectal) may be superior in achieving clinical remission compared to placebo (oral and rectal) (14/87 participants with tacrolimus versus 1/61 participants with placebo; risk ratio (RR) 3.76, 95% confidence interval (CI) 1.03 to 13.73; 3 studies). These results are of low certainty due to imprecision and risk of bias.

BMC Medical Education

RESEARCH

Open Access

# Assessment of an intensive education program for pharmacists on treatment of tobacco use disorder using an objective structured clinical examination: a randomized controlled trial

Maguy Saffouh El Hajj[1*], Ahmed Awaisu[1], Mohamad Haniki Nik Mohamed[2], Rana Ahmed Saleh[1], Noora Mohammed Al Hamad[3], Nadir Kheir[4] and Ziyad R. Mahfoud[5,6]

## Abstract

**Background:** Tobacco use is one of the major public health threats globally. Community pharmacists are uniquely positioned to offer tobacco cessation services owing to their easy accessibility by the public. To prepare Qatar community pharmacists to develop the competencies and skills required to offer smoking cessation services, an intensive tobacco control education program was designed and implemented. The study aimed to assess the impact of the tobacco education program on the pharmacists' skills and competence.

**Methods:** A random sample of community pharmacists in Qatar was chosen for participation in the program. Consenting participants were randomly assigned to either intervention or control groups. The intervention group received an intensive education program on treatment of tobacco-use disorder, while a short didactic session on a non-tobacco-related topic was delivered to the control group. The pharmacists' tobacco cessation skills and competencies were assessed using an Objective Structured Clinical Examination (OSCE).

**Results:** A total of 54 and 32 community pharmacists in the intervention group and the control group, respectively, completed the OSCE. The intensive tobacco education group achieved significantly higher total scores than the control group in all the OSCE cases. Specifically, the mean total scores for the intervention group were 15.2, 15.3, 14.2, 14.6, 16.3, and 15.2 compared to 8.8, 6.2, 7.7, 9.2, 8.3, and 11.3 for the control group ($p < 0.001$) for cases one to six respectively.

**Conclusion:** The study demonstrated that an intensive tobacco cessation education program can improve pharmacists' tobacco cessation skills and increase their tobacco cessation counseling abilities.

**Trial registration:** Clinical Trials NCT03518476 (https://clinicaltrials.gov/ct2/show/NCT03518476) Registration date: May 8, 2018.

**Keywords:** Qatar, Education program, Tobacco control, Smoking cessation, Pharmacist, OSCE

## Background

Around 942 million men and 175 million women aged 15 or older currently smoke cigarettes globally [1]. About three-quarters of male daily smokers reside in countries

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# Amino Acid PET Imaging with $^{18}$F–DOPA in the evaluation of Pediatric Brain Tumors

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Affiliations + expand

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## Abstract

Although MRI is the workhorse of brain tumor initial evaluation and follow-up, there is a growing amount of data recommending the incorporation of amino-acid PET imaging at different stages of the management of these patients. Recent nuclear medicine and neuro-oncology clinical practice recommendations support the use of amino-acid imaging in brain tumor imaging. Considering $^{18}$F-DOPA is FDA approved for the evaluation of parkinsonian syndromes, it could be used clinically for other valuable clinical indications such as brain tumor evaluations. This value seems to be well established in adults and has growing evidence for its use in pediatrics as well. We offer to present four pediatric brain tumor cases imaged with $^{18}$F-DOPA and review the literature.

**Keywords:** Correlative Imaging; MRI; Molecular Imaging; Oncology: Brain; PET; PET/CT; PET/MRI; Pediatrics; Radiation Therapy Planning; amino acid imaging; brain tumors; nuclear medicine.

diagnostics

MDPI

*Article*

# QUCoughScope: An Intelligent Application to Detect COVID-19 Patients Using Cough and Breath Sounds

**Tawsifur Rahman [1], Nabil Ibtehaz [1], Amith Khandakar [1], Md Sakib Abrar Hossain [1], Yosra Magdi Salih Mekki [2], Maymouna Ezeddin [1], Enamul Haque Bhuiyan [3], Mohamed Arselene Ayari [4], Anas Tahir [1], Yazan Qiblawey [1], Sakib Mahmud [1], Susu M. Zughaier [2], Tariq Abbas [5], Somaya Al-Maadeed [6] and Muhammad E. H. Chowdhury [1,*]**

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**Abstract:** Problem—Since the outbreak of the COVID-19 pandemic, mass testing has become essential to reduce the spread of the virus. Several recent studies suggest that a significant number of COVID-19 patients display no physical symptoms whatsoever. Therefore, it is unlikely that these patients will undergo COVID-19 testing, which increases their chances of unintentionally spreading the virus. Currently, the primary diagnostic tool to detect COVID-19 is a reverse-transcription polymerase chain reaction (RT-PCR) test from the respiratory specimens of the suspected patient, which is invasive and a resource-dependent technique. It is evident from recent researches that asymptomatic COVID-19 patients cough and breathe in a different way than healthy people. Aim—This paper aims to use a novel machine learning approach to detect COVID-19 (symptomatic and asymptomatic) patients from the convenience of their homes so that they do not overburden the healthcare system and also do not spread the virus unknowingly by continuously monitoring themselves. Method—A Cambridge University research group shared such a dataset of cough and breath sound samples from 582 healthy and 141 COVID-19 patients. Among the COVID-19 patients, 87 were asymptomatic while 54 were symptomatic (had a dry or wet cough). In addition to the available dataset, the proposed work deployed a real-time deep learning-based backend server with a web application to crowdsource cough and breath datasets and also screen for COVID-19 infection from the comfort of the user's home. The collected dataset includes data from 245 healthy individuals and 78 asymptomatic and 18 symptomatic COVID-19 patients. Users can simply use the application from any web browser without installation and enter their symptoms, record audio clips of their cough and breath sounds, and upload the data anonymously. Two different pipelines for screening were developed based on the symptoms reported by the users: asymptomatic and symptomatic. An innovative and novel stacking CNN model was developed using three base learners from of eight state-of-the-art deep learning CNN algorithms. The stacking CNN model is based on a logistic regression classifier meta-learner that uses the spectrograms generated from the breath and cough sounds of symptomatic and asymptomatic patients as input using the combined (Cambridge and collected) dataset. Results—The stacking model outperformed the other eight CNN networks with the best classification performance for binary classification using cough sound spectrogram images. The accuracy, sensitivity, and specificity for symptomatic and asymptomatic patients were 96.5%, 96.42%, and 95.47% and 98.85%, 97.01%, and 99.6%, respectively. For breath sound spectrogram images, the metrics for binary classification

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# Comprehensive human amniotic fluid metagenomics supports the sterile womb hypothesis

HanChen Wang[1,2], Gui Xiang Yang[1], Yuxiang Hu[3,4], Patricia Lam[1,5], Karan Sangha[1], Dawn Siciliano[1], Anne Swenerton[1], Ruth Miller[6,7,8], Peter Tilley[6,7], Peter Von Dadelszen[3,9], Shirin Kalyan[10], Patrick Tang[6,7,11] & Millan S. Patel[12,13]✉

**As metagenomic approaches for detecting infectious agents have improved, each tissue that was once thought to be sterile has been found to harbor a variety of microorganisms. Controversy still exists over the status of amniotic fluid, which is part of an immunologically privileged zone that is required to prevent maternal immune system rejection of the fetus. Due to this privilege, the exclusion of microbes has been proposed to be mandatory, leading to the sterile womb hypothesis. Since nucleic acid yields from amniotic fluid are very low, contaminating nucleic acid found in water, reagents and the laboratory environment frequently confound attempts to address this hypothesis. Here we present metagenomic criteria for microorganism detection and a metagenomic method able to be performed with small volumes of starting material, while controlling for exogenous contamination, to circumvent these and other pitfalls. We use this method to show that human mid-gestational amniotic fluid has no detectable virome or microbiome, supporting the sterile womb hypothesis.**

Bacterial or viral invasion of the amniotic cavity has been associated with fetal loss, birth defects, fetal anemia, preterm premature rupture of membranes, preterm labor and birth, and maternal mortality[1–5]. Intact chorioamniotic membranes are essential to prevent invasion, as the majority of mothers will develop microbial invasion of the amniotic cavity (MIAC) after membrane rupture[6,7]. This observation, along with the inevitability of preterm birth after MIAC, illustrates that the amniotic cavity has a limited ability to combat active infection. This has been proposed, in part, to be due to the maternal immunologic privilege afforded the fetus, which must be maintained to prevent rejection of the pregnancy by the maternal immune system. Both the immune privilege and the intolerance for MIAC have led to the proposal that amniotic fluid must be sterile, known as the sterile womb hypothesis. Evidence documenting this sterility was first provided by Escherich[8].

Addressing this hypothesis and understanding the full impact of infection in pregnancy requires development of methods capable of the unbiased detection of all potential pathogens in samples from affected pregnancies. To this end, a variety of methods have been developed with various degrees of sensitivity and specificity, including: Degenerate Oligonucleotide Primed PCR[9], Virus Discovery based on cDNA Amplified Fragment Length Polymorphism (VIDISCA)[10,11], the Virochip[12], Comprehensive serological profiling[13], or large scale multiplexed qPCR[14]. Each of these methods has different limitations such as low sensitivity (up to $10^6$ genome copies/mL) in biological fluids for some, requirement for large scale and ongoing assay development, or lack of flexibility. Recently, massively parallel metagenomic sequencing methods have been used to suggest the presence of microbial nucleic acid in amniotic fluid[15,16], placenta[17], umbilical cord blood[18] and meconium[19,20]. However, other studies have disputed these findings in placenta[21,22] and amniotic fluid[23–26].

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GLOBAL ONCOLOGY: RESEARCH ARTICLE

# Building the ecosystem for pediatric neuro-oncology care in Pakistan: Results of a 7-year long twinning program between Canada and Pakistan

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## Abstract

**Background:** Low- and middle-income countries sustain the majority of pediatric cancer burden, with significantly poorer survival rates compared to high-income countries. Collaboration between institutions in low- and middle-income countries and high-income countries is one of the ways to improve cancer outcomes.

**Methods:** Patient characteristics and effects of a pediatric neuro-oncology twinning program between the Hospital for Sick Children in Toronto, Canada and several hospitals in Karachi, Pakistan over 7 years are described in this article.

**Results:** A total of 460 patients were included in the study. The most common primary central nervous system tumors were low-grade gliomas (26.7%), followed by medulloblastomas (18%), high-grade gliomas (15%), ependymomas (11%), and craniopharyngiomas (11.7%). Changes to the proposed management plans were made in consultation with expert physicians from the Hospital for Sick Children in Toronto, Canada. On average, 24% of the discussed cases required a change in the original management plan over the course of the twinning program. However, a decreasing trend in change in management plans was observed, from 36% during the first 3.5 years to 16% in the last 3 years. This program also led to the launch of a national pediatric neuro-oncology telemedicine program in Pakistan.

**Abbreviations:** AKUH, Aga Khan University Hospital; CNS, central nervous system; HICs, high-income countries; IARC, International Agency for Research on Cancer; ICCH, Indus Children Cancer Hospital; KHCC, King Hussein Cancer Center; LMICs, low- and middle-income countries; MDTB, multidisciplinary tumor board; CMMRD, constitutional mismatch repair deficiency; SDI, sociodemographic index; SJCRH, St. Jude Children's Research Hospital.

  

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# A Novel Homozygous *MC2R* Variant Leading to Type-1 Familial Glucocorticoid Deficiency

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## Abstract

**Context:** Type 1 familial glucocorticoid deficiency (FGD) (OMIM #607397) is a rare autosomal recessive disorder due to mutations in melanocortin-2-receptor (MC2R) gene encoding the G protein-coupled adrenocorticotropic (ACTH) transmembrane receptor.

**Objective:** The aim of the study is to describe 2 siblings born to a healthy consanguineous family presenting with clinical and biochemical features of FGD, harboring a novel homozygous MC2R variant.

**Methods:** Both patients are siblings born at term via normal delivery with normal birth weights. The first sibling presented with symptoms of hypoglycemia, repeated episodes of infections starting from 2 days of age. At 18 months of age, low serum cortisol was found, and he was started on hydrocortisone replacement therapy. The second sibling developed hypoglycemia on day 1 after birth, investigations revealed low serum sodium and cortisol levels and was also commenced on hydrocortisone treatment. Whole exome sequencing (WES) and in vitro functional studies on cell line transfected with wild-type and mutant plasmid clones were undertaken.

**Results:** WES revealed a novel homozygous missense mutation c.326T>A, p.Leu109Gln in the MC2R gene. In-silico prediction tools predicted the effect of this mutation to be deleterious. In vitro study using HEK293 cells transfected with MC2R wild-type and mutant clones showed a defect in protein expression and cAMP generation when stimulated with ACTH.

**Conclusion:** Homozygous semiconserved p.Leu109Gln mutation disrupts cAMP production and MC2R protein expression leading to ACTH resistance. This study provides additional evidence that this novel pathogenic variant in MC2R results in FGD phenotypes.

**Key Words:** MC2R, ACTH, adrenal insufficiency, familial glucocorticoid deficiency, next-generation sequencing

**Abbreviations:** ACTH, adrenocorticotropic hormone; cAMP, cyclic adenosine monophosphate; DMEM, Dulbecco's Modified Eagle Medium; FGD, familial glucocorticoid deficiency; GPCR, G protein coupled receptor; MC2R, melanocortin-2 receptor; MRAP, melanocortin-2 receptor accessory protein; PCR, polymerase chain reaction; TSH, thyrotropin (thyroid-stimulating hormone); WES, whole exome sequencing.

Familial glucocorticoid deficiency (FGD) (OMIM #202200), also known as isolated glucocorticoid deficiency, or hereditary unresponsiveness to adrenocorticotropin hormone (ACTH), is an autosomal recessive disorder due to a failure of the action of ACTH to stimulate the adrenal gland to produce glucocorticoids [1]. FGD was first reported in 2 sisters in 1959 by Shepard and colleagues [2] and is characterized by high plasma ACTH levels and severe cortisol deficiency. If left untreated, FGD can be lethal and may lead to death due to hypoglycemia, increased susceptibility to infections, hyperpigmentation, and seizures [3].

FGD is a heterogeneous disorder with multiple subtypes. The 2 most common subtypes are FGD type 1 (OMIM #607397) and FGD type 2 (OMIM #609196). Mutations in melanocortin-2 receptor (*MC2R*) cause FGD type 1 while mutations in its accessory protein, melanocortin-2 receptor accessory protein (*MRAP*) lead to FGD type 2. Mutations in both *MC2R* and *MRAP* genes account for 40% to 55% of FGD cases [4]. Even though MC2R and MRAP are the 2 most common causes of FGD, due to advances in genome sequencing, recently several other genes which lead to adrenal insufficiency have been identified. These genes include minichromosomal maintenance-4 deficiency (*MCM4*) [5], nicotinamide nucleotide transhydrogenase (*NNT*) [6], steroid acute regulatory (*STAR*) [7], thioredoxin reductase 2 (*TXNRD2*) [8], and sphingosine-1-phosphate lyase (*SGPL1*) [9].

Five melanocortin receptors (MC1R to MC5R) have been identified so far. These receptors consist of 7 transmembrane G protein coupled receptors (GPCRs), which are closely related in structure and share homology at the amino acid level [10]. Melanocortin receptors show overlapping specificities to ligand affinity and they bind to several melanocortins, α-MSH, β-MSH, γ-MSH, δ-MSH, and ACTH; only MC2R shows high selectivity for adrenocorticotropic hormone (ACTH) [11]. The human MC2R, also known as ACTH receptor, located on chromosome 18p11.21, is the smallest GPCR, encoding a 297-amino acid protein with a molecular weight of around 33 kDa [12]. MC2R is predominantly expressed in all 3 layers of the adrenal cortex; zona reticularis and zona fasciculata stimulate the secretion of glucocorticoids while zona glomerulosa stimulates the secretion of aldosterone. MC2R activation by ACTH leads to an increase in cyclic adenosine monophosphate (cAMP) and protein kinase A, subsequently activating the steroidogenic enzymes expression pathway [13]. MC2R inactivating mutations lead to low levels of cortisol and high levels of plasma

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Observational Study

Medicine

OPEN

# The correlation between middle schoolchildren allergic symptoms and airborne particle season

## A cross-sectional study

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**Abstract**

Limited studies correlate allergic symptoms and associated outdoor biological particle exposure among schoolchildren globally.

This study aimed to investigate the relationship between the seasonality of symptoms of allergic diseases among middle schoolchildren and the annual variation of airborne pollen and fungal spore in a hot and humid geographical region (Qatar).

During November 2017 to January 2018, a self-reported study of middle schoolchildren living in the Doha capital city of Qatar was conducted, and data gathered were evaluated in relation to the collected monthly pollen and fungal spores. Participants' data were collected by conducting a survey based on a modified questionnaire adopted from the International Study of Asthma and Allergy in Childhood (ISAAC). The airborne pollen and fungal spore in Doha's atmosphere were extracted from the Doha aerobiology project (2017–2020).

Among the 1000 distributed questionnaires, 100 were excluded due to significant missing data and 644 middle schoolchildren living in Doha city responded and were included in the final analysis. The symptoms of allergic rhinitis (AR) pattern among the responders with positive symptoms were strongly linked with the higher airborne fungal spore incidence during the month of November. Out of 331 students with positive symptoms, the prevalence of AR, lifetime wheeze, and eczema was 62.8%, 28.1%, and 26.6%, respectively. Asthma was significantly higher in Qatari (39.8%) compared to non-Qatari (26.7%) middle schoolchildren ($P = .02$).

Outdoor aeroallergen may be a contributing factor in addition to other environmental and genetic predisposing factors for childhood atopic diseases in the prevalence rate of allergic symptoms among middle schoolchildren in the peninsula of Qatar.

**Abbreviations:** AR = allergic rhinitis, ISAAC = The International Study of Asthma and Allergies in Children.

**Keywords:** airborne aeroallergens, allergic rhinitis, asthma, eczema, middle schoolchildren

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*Consent for publication: We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of the authors listed in the manuscript has been approved by all of the authors. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In doing so, we confirm that we have followed the regulations of our institutions concerning intellectual property. We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. We understand that the corresponding author is the sole contact for the editorial process (including the editorial manager and direct communications with the office). She is responsible for communicating with the other authors about the progress, submission of revisions, and the final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the corresponding author.*

*Availability of data and materials: The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.*

*Ethics approval and consent to participate: The study was approved by the Ethical Committee of the Hamad Medical Corporation, Doha, Qatar (MRC#16150/16). All clinical investigations were conducted according to the principles expressed in the 1964 Helsinki declaration and its recent amendments. The present study is part of a bigger Qatar National Research Fund Project and was involving middle schoolchildren in an anonymous survey but no patients or animals. However, the whole QNRF project was associated with patients' data and written informed consent was obtained from all the participants in the project accordingly.*

*Competing interest: There are no commercial associations that might pose a conflict of interest.*

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*All data generated or analyzed during this study are included in this published article (and its supplementary information files).*

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Neonatology

Systematic Review

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# Multisystemic Inflammatory Syndrome in Neonates: A Systematic Review

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**Keywords**
Neonate · Multisystem inflammatory · Severe acute respiratory syndrome coronavirus-2 · COVID-19 · Multisystem inflammatory syndrome

**Abstract**
***Introduction:*** Multisystem inflammatory syndrome in neonates (MIS-N) related to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has increasingly been reported worldwide amid the spread of the SARS-CoV-2 pandemic.
***Methods:*** We searched PubMed, EMBASE, and CINAHL and preprint servers (BioRxiv.org and MedRxiv.org) using a specified strategy integrating Medical Subject Headings terms and keywords until October 20, 2021. Our aim was to systematically review demographic profiles, clinical features, laboratory parameters, complications, treatments, and outcomes of neonates with MIS-N. Studies were selected when fulfilling the inclusion criteria. Articles were included if they fulfilled the World Health Organization (WHO), Centers for Disease Control (CDC) definitions of MIS-C, or our proposed definition. ***Results:*** Sixteen reports of MIS-N including 47 neonates meeting MIS-N criteria were identified. Presentation included cardiovascular compromise (77%), respiratory involvement (55%), and fever in (36%). Eighty-three percent of patients received steroids, and 76% received immunoglobulin. Respiratory support was provided to 60% of patients and inotropes to 45% of patients. Five (11%) neonates died. ***Conclusion:*** The common presentation of MIS-N included cardiorespiratory compromise with the possibility of high mortality. Neonates with MIS-N related to SARS-CoV-2 may be at higher risk of adverse outcomes.



## Introduction

As the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic continues worldwide, increasing cases of severe disease are being reported, including multisystem inflammatory syndrome in children (MIS-C) [1]. Similar to macrophage activating syndrome

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PEDIATRIC ONCOLOGY

# International Comparisons of Clinical Demographics and Outcomes in the International Society of Pediatric Oncology Wilms Tumor 2001 Trial and Study

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**PURPOSE** International comparisons of patient demographics, tumor characteristics, and survival can shed light on areas for health care system improvement. The International Society of Pediatric Oncology Wilms Tumor 2001 trial/study registered patients through national clinical study groups in Western Europe and Brazil. This retrospective post hoc analysis of the International Society of Pediatric Oncology Wilms Tumor 2001 database aims to make visible and suggest reasons for any variations in outcomes.

**METHODS** All patients with unilateral Wilms tumor (WT), age > 6 months, treated with preoperative chemotherapy as per protocol, and registered between 2001 and 2011 were eligible. Countries were grouped to give comparable case numbers and geographical representation. Cox univariable and multivariable (MVA) statistics were applied, with the German collaborative group (Gesellschaft für Pädiatrische Onkologie und Hämatologie—Austria, Germany, and Switzerland) as reference for hazard ratios for event-free survival (EFS) and overall survival (OS).

**RESULTS** A total of 3,176 eligible patients were registered from 24 countries assigned into six groups. Age and histologic risk group distribution were similar across all groupings. The distribution of WT stage varied by country grouping, with 14.9% (range, 11.1%-18.2%) metastatic at diagnosis. Median follow-up was 78.9 months. For localized WT, 5-year EFS varied from 80% (Brazilian group) to 91% (French group; $P < .0001$), retaining significance only for Brazil in MVA ($P = .001$). Five-year OS varied from 89% (Brazilian group) to 98% (French group; $P < .0001$). In MVA, only superior OS in France was significant ($P = .001$). Five-year EFS/OS for stage IV did not vary significantly. High-risk histology and tumor volume at surgery were significantly associated with increased risk of death in MVA for metastatic disease.

**CONCLUSION** International benchmarking of survival rates from WT within a large trial/study database has demonstrated statistically significant differences. Clinical interpretation should take account of variation in tumor stage but also treatment factors.

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ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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## INTRODUCTION

International comparisons of cancer survival rates can highlight areas for health care improvement.[1] These include opportunities for earlier diagnosis, reducing variation in how standardized treatments are applied, and revealing differences in tumor biology between populations. Ideally, such comparisons use population-based cancer registry data to avoid any selection bias in the study cohorts.[2] The disadvantage of using cancer registry data is that they often lack relevant details of patient demographics and tumor characteristics used for clinical risk stratification, treatments given, and if relapse occurred.

Childhood cancer survival rates vary widely between countries and world regions.[3] Many factors account for these disparities, including national income status (World Bank country classifications by income level), characteristics of health care systems, accuracy of diagnosis and risk stratification, quality of treatment, supportive care, proportion of patients included in trials, and differences in tumor biology.[4,5]

Clinical trial data sets can be used for such comparisons, particularly in childhood cancers where the clinical community has a history of enrolling a high proportion of all cases into international cooperative group studies. Such within-trial comparative analyses

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ORIGINAL CONTRIBUTIONS

Experimental ONCOLOGY

# A LONG-TERM 10G-HYPERGRAVITY EXPOSURE PROMOTES CELL-CELL CONTACTS AND REDUCES ADHESIVENESS TO A SUBSTRATE, MIGRATION, AND INVASIVENESS OF MCF-7 HUMAN BREAST CANCER CELLS

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***Background*: G-force is a fundamental force controlling human cells. Cancer is one of the 4 major health challenges in the Space missions. Cancer in Space project evaluates the reaction of human cancer cells to the conditions of the space flights, including an exposure to high g-forces. *Aim*: Explore an impact of 10 g force on the oncogenic properties of human breast adenocarcinoma cells MCF-7. *Materials and Methods*: Cells were exposed to 10 g force for 10 days, as part of a 6-week simulation of conditions of a space flight. Then the cells were cultured for one week under normal culture conditions, before performing tests. Cell proliferation, cell viability, cell-cell contact inhibition, migration, and invasiveness were measured. Immunoblotting was used to evaluate expression of proteins. *Results*: Proliferation, cell-cell interaction and formation of 3D structures, migration, and invasiveness of cells exposed to 10 g were compared to parental cells cultured at 1 g condition. 10 g exposed cells showed a higher propensity for cell-cell contact inhibitions and lower for 3-dimensional growth in dense culture. This correlated with the decrease of proliferation in a dense culture as compared to the parental cells. The decrease of migration, adherence to a surface, and invasiveness was observed for cells subjected to the hypergravity, as compared to the parental MCF-7 cells. Enhanced expression of E-cadherin and phosphorylated pY576-FAK were observed in 10 g exposed cells but no impact on the expression of Erk, pErk, FAK and p53 was detected. *Conclusion*: The prolonged exposure of MCF-7 cells to 10 g force targets cell-cell and cell-substrate interactions.**
***Key Words*: g-force, hypergravity, human cancer cells, MCF-7, cell-cell interaction, cell-substrate interaction.**

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G-force is one of the fundamental forces controlling cellular physiology. Definition of the weight and masses of cells and cellular components defines regulatory mechanisms in cells [1–4]. Directionality and the strength of g-force impacts the cell growth, death, and migration of human cells [1, 4]. Space research has focused on studies of effects of the weightlessness defined as microgravity. The impact of high gravity force on human cells is much less explored.

Studies of the biological impact of gravity are crucial for two reasons. The first is related to the exposure of humans to high g forces in the space or on Earth, e.g., during flights. The second reason is a study of fundamental mechanisms controlling human cells in normal and disease conditions. Gravity is a fundamental force that has been without significant fluctuations during the whole history of life on Earth. The role of the gravity force is crucial in the definition of living systems, e.g., the size of organisms, biochemical processes and physiology [1–4].

Gravity-sensing mechanisms have been studied in human, animal, and plant cells (reviewed in Takahashi *et al*. [4]). On the cellular level, response to gravity includes modulation of the cytoskeleton, cell-cell and cell-substrate interactions, and on the intracellular level a number of regulatory pathways were identified [5–10]. Changes in cellular adhesion and cytoskeleton are among the most frequently observed effects of gravity, e.g., modulation of vessel formation by endothelial cells [11, 12]. Promotion of myoblasts differentiation [13], neuron-like differentiation of PC12 cells [14], and decreased count of $CD4^+CD8^+$ thymocytes [15] were observed upon exposure to hypergravity. Among response mechanisms to hypergravity, there were reported cAMP-reactive proteins [16], and c-fos, ROCK/Rho-GTP, and the PI3K signaling [17]. Enhanced release of reactive oxygen species upon exposure to hypergravity was also reported [18]. Omics studies, e.g., sequencing data, showed that 15 min of hypergravity induced expression of a significant number of genes, e.g., ATPase subunits and the cluster of differentiation molecules [19]. However, most of the altered gene expression was transient [19, 20]. This suggests that a longer exposure to hypergravity has to be studied to detect permanently acquired changes.

A number of studies showed that human cancer cells react to hypergravity in a way that affects their oncogenic properties. Stress signaling response, inhibition of cell proliferation, and modified patterns of cell-cell interaction and migration were observed [5–8, 21, 22]. However, the available data

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*Abbreviations used*: CBB – coomassie brilliant blue; FAK – focal adhesion kinase.

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RESEARCH ARTICLE
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MICROBIOLOGY SOCIETY
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# Reporting of RT-PCR cycle threshold (Ct) values during the first wave of COVID-19 in Qatar improved result interpretation in clinical and public health settings

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**Abstract**

**Introduction.** The cycle threshold (Ct) value in real-time PCR (RT-PCR) is where a target-specific amplification signal becomes detectable and can infer viral load, risk of transmission and recovery. Use of Ct values in routine practice is uncommon.

**Gap Statement.** There is a lack of routine use of Ct values when reporting RT-PCR results in routine practice.

**Aim.** To automatically insert Ct values and interpretive comments when reporting SARS-CoV-2 RT-PCR to improve patient management.

**Methodology.** Routine Ct values across three different RT-PCR platforms were reviewed for concordance at presentation and clearance in patients with COVID-19. An indicative threshold (IT) linked to viral clearance kinetics was defined at Ct30 to categorize Ct values as low and high, reflecting high and low viral loads respectively.

**Results.** The different gene targets of each platform showed high correlation and kappa score agreement ($P$<0.001). Average Ct values were automatically generated with values ≤Ct30 reported as positive and >Ct30 as reactive; interpretive comments were added to all reports. The new reporting algorithm impacted on: physician interpretation of SARS-CoV-2 results; patient management and transfer; staff surveillance; length of stay in quarantine; and redefinition of patient recovery.

**Conclusion.** Incorporation of Ct values into routine practice is possible across different RT-PCR platforms and adds useful information for patient management. The use of an IT with interpretive comments improves clinical interpretation and could be a model for reporting other respiratory infections. Withholding Ct values wastes useful clinical data and should be reviewed by the profession, accreditation bodies and regulators.

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**Keywords:** cycle threshold; real-time PCR (RT-PCR); SARS-CoV-2; COVID-19.
**Abbreviations:** CAP, College of American Pathologists; CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus infectious disease 2019; CrI, credible interval; Ct, cycle threshold; HCoV, human coronavirus; IT, interpretive threshold; NPS/OPS, nasopharyngeal / oropharyngeal Swab; RT-PCR, reverse transcriptase PCR; WHO, World Health Organization.
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[Intervention Review]

# Antibiotics for the induction and maintenance of remission in ulcerative colitis

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## ABSTRACT

### Background

Antibiotics have been considered to treat ulcerative colitis (UC) due to their antimicrobial properties against intestinal bacteria linked to inflammation. However, there are concerns about their efficacy and safety.

### Objectives

To determine whether antibiotic therapy is safe and effective for the induction and maintenance of remission in people with UC.

### Search methods

We searched five electronic databases on 10 December 2021 for randomised controlled trials (RCTs) comparing antibiotic therapy to placebo or an active comparator.

### Selection criteria

We considered people with UC of all ages, treated with antibiotics of any type, dose, and route of administration for inclusion. Induction studies required a minimum duration of two weeks for inclusion. Maintenance studies required a minimum duration of three months to be considered for inclusion.

### Data collection and analysis

We used standard methodological procedures expected by Cochrane. Our primary outcome for induction studies was failure to achieve remission and for maintenance studies was relapse, as defined by the primary studies.

### Main results

We included 12 RCTs (847 participants). One maintenance of remission study used sole antibiotic therapy compared with 5-aminosalicylic acid (5-ASA). All other trials used concurrent medications or standard care regimens and antibiotics as an adjunct therapy or compared antibiotics with other adjunct therapies to examine the effect on induction of remission.

There is high certainty evidence that antibiotics (154/304 participants) compared to placebo (175/304 participants) result in no difference in failure to achieve clinical remission (risk ratio (RR) 0.88, 95% confidence interval (CI) 0.74 to 1.06). A subgroup analysis found no differences when steroids, steroids plus 5-ASA, or steroids plus 5-ASA plus probiotics were used as additional therapies to antibiotics and placebo.

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WILEY

HOW I APPROACH

# How we approach paediatric renal tumour core needle biopsy in the setting of preoperative chemotherapy: A Review from the SIOP Renal Tumour Study Group

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## Abstract

The International Society of Paediatric Oncology Renal Tumour Study Group (SIOP-RTSG) advocate treating children with Wilms tumour (WT) with preoperative chemotherapy, whereas the Renal Tumor Committee of the Children's Oncology Group (COG) advocates primary nephrectomy (without biopsy) when feasible. Successive SIOP-RTSG trial protocols recommended pretreatment biopsy of children with unilateral tumours only where there were features to suggest an increased probability of a non-WT requiring a change in management. The UK experience in the SIOP WT 2001 trial showed that an alternate approach of performing biopsies on all

**Abbreviations:** CCSK, clear cell sarcoma of the kidney; CN, cystic nephroma; CNB, core needle biopsy; COG, Children's Oncology Group; CPDN, cystic partially differentiated nephroblastoma; FNA, fine-needle aspiration; GPOH, Gesellschaft für pädiatrische Onkologie und Hämatologie; ICCC, International Classification of Childhood Cancer; MN, mesoblastic nephroma; RCC, renal cell carcinoma; RTK, rhabdoid tumour of the kidney; SIOP-RTSG, International Society of Paediatric Oncology Renal Tumour Study Group; TBM, tumour board meeting; WT, Wilms tumour; XGP, xanthogranulomatous pyelonephritis.

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CASE REPORT

# Type 2 Diabetes Mellitus in a 7 Year Old Girl

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**Abstract:** Type 2 diabetes is a chronic disease due to insulin resistance resulting in hyperglycemia. The prevalence of type 2 diabetes is increasing worldwide in the pediatric population. In the pediatric population, type 2 diabetes typically develops around adolescence; however, patients with a younger age of onset are now being reported. Earlier onset of type 2 diabetes is associated with a more aggressive course of disease and earlier comorbidities, although data on this is limited. We report a child from Qatar with type 2 diabetes that was diagnosed at 7 years of age, along obesity with a BMI of 26.8 kg/m$^2$. Elevated liver enzymes, c-peptide, and insulin levels were observed along with fatty liver on an ultrasound. The child had severe acanthosis nigricans with increased appetite. There was a positive family history for type 2 diabetes. Testing for type 1 diabetes autoantibodies, monogenic obesity, and monogenic diabetes screening was negative. This is the second youngest child reported to have type 2 diabetes. Accurate diagnosis, early reporting, and long-term follow-up of such cases is necessary to bring more attention to the subgroup of type 2 diabetes in very young patients.

**Keywords:** pediatric diabetes, type 2 diabetes, insulin resistance, early-onset diabetes mellitus

## Introduction

Diabetes mellitus is on the rise in adults as well as in the pediatric population, with an estimated 3% rise annually.[1] Although type 1 diabetes is the most common type of diabetes in children, the incidence of type 2 diabetes, which was thought to be uncommon in children, is also increasing.[2] Sweden, which is one of the countries with the highest prevalence of children with diabetes in the world, reported the incidence of type 2 diabetes in children as 3.1 per 100,000 per year.[3] In Qatar, the reported prevalence is 23.7 per 100,000 for children with type 2 diabetes living in the country and an incidence of 2.51 in 2020.[4] In 2019, the US reported 283,000 individuals under 20 years diagnosed with type 2 diabetes and an incidence of 5,800 new cases in 2014–2015.[5]

In the pediatric population, the onset of type 2 diabetes is most often around the adolescence period, however, there are rare reports of type 2 diabetes developing in children as young as 5 and 8 years of age.[6,7] The cause of such early onset type 2 diabetes in childhood is not yet known but might be related to the increasing obesity epidemic seen all over the world, the sedentary lifestyle, possible underlying genetic factors, or as yet unknown factors. The SEARCH for Diabetes in Youth study estimated an overall increase of 30.5% in the prevalence of type 2 diabetes in youth. Out of all children with type 2 diabetes in the 2009 SEARCH database, 2.4% were <10 years of age.[8]

Here we report the youngest patient with type 2 diabetes from Qatar, with the age of onset at 7 years of age, and describe the clinical and biochemical findings observed.

## Case Presentation

We present an 8 year old girl of Sri Lankan ethnicity. She was born at term with a birth weight of 2.45 kg and length of 49 cm. There was no history of any complications including gestational diabetes during the pregnancy. There were no medical concerns in the postnatal or early childhood phases. At the age of 6 years of age the patient was diagnosed with obesity after the parents noted that the child was gaining weight rapidly and getting tired very easily. There was also a history of snoring at night but no apnoea. She presented to the hospital at 7 years of age for these symptoms and was

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Short Communication

# The impact of dependence on advanced imaging techniques on the current radiology practice

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ABSTRACT

Medical imaging techniques are a helpful tool for physicians to diagnose and treat diseases. Some of these techniques are conventional and include X-rays, Ultrasounds while others are advanced imaging modalities such as MRI and CT scans. Recently, more and more physicians are relying on these advanced imaging modalities because of advancements in technology, increased patient demand, greater finances, and the fear of any malpractice suits in case of missed diagnosis. While these techniques, no doubt, offer a quicker and correct diagnosis owing to their sharp resolution and sensitivity, they do expose the patient to a great source of radiation, are expensive, time consuming, and are not an ideal means to be used in all situations. Thus, it is crucial to mitigate their unnecessary use. The following article focuses on the growing use of such techniques, their advantages and disadvantages and how to alleviate their exaggerated use.

Medical imaging techniques aid in the diagnosis and treatment of both adult and children population [1], and lately there has been a rise in the use of medical imaging techniques for the purposes of diagnosis and follow up of diseases [2]. It is important to acknowledge the fact that where imaging facilities pave the way for diagnosis and treatment, they do have some drawbacks such as higher costs and disadvantages to patients in case of an incidental finding, aggressive diagnosis, unnecessary anxiety and, and radiation exposure [3].

The rise in the use of imaging facilities can be due to advancements in technology, increased demand by physicians and patients, and greater financial means [3]. There has been a rise of 8% use of computed tomography (CT) scans in the last decade or so [4]. A study showed that between 2001 and 2010 the rates of CT scans done in emergency department quadrupled for patients with respiratory symptoms but regarded such rise in the number of CT scans in emergency settings as useless [4]. In Ontario and 7 integrated healthcare systems of United States (US), use of CT, magnetic resonance imaging (MRI) and ultrasound have increased, with the greatest annual growth occurred between years 2000–2006 and sustained growth between 2012 and 2016 (1–5% annually) for almost all ages [3]. About 30% of imaging examination is deemed needless, and contributes $30 billion annually in US [3].

The advancement in technology has encouraged the physicians to order more CT scans and MRI for the conditions used to be investigated with more basic imaging techniques [5]. CT scan provides a better view of the pathologies than a plain radiograph. For instance, CT pulmonary angiography is the single best imaging technique to identify and follow the work up on pulmonary embolism due to its high resolution and fast speed, and thus summates the expenditure on chest imaging [5]. CT scan with its greater specificity and sensitivity and increased visualization ability can pick up small opacities missed on chest x-rays, and better view certain regions such as lung bases and lingula [10]. Enhanced resolution of advanced modalities also helps rule out the possibility of cancer in doubtful lesions, thus greater number of tests are being

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QUANTITATIVE RESEARCH

# Factors associated with intention to receive vaccines for bacterial sexually transmitted infections among young HPV-vaccinated Canadian women

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## Abstract

**Objective** The aim of this study was to explore the acceptability of bacterial STI vaccines among young HPV-vaccinated Canadian women to inform future vaccine program implementation.

**Methods** A 20-item cross-sectional questionnaire was administered from June 2019 to June 2020 to HPV-vaccinated participants of the pan-Canadian QUEST cohort. Multivariable logistic regression models assessed interest in chlamydia, syphilis, and gonorrhea vaccines using a priori variables and factors significant in bivariate analysis.

**Results** Of the 1092 respondents analyzed, 82% indicated interest in receiving one or more future STI vaccines. Respondents had a median age of 19.6 years (range 16.9–23.4), and 75% of respondents identified as white/European descent. In adjusted analyses, intent to engage in positive health behaviours was associated with vaccine interest for syphilis (OR = 5.76, 95% CI 4.03–8.27), chlamydia (OR = 5.27, 95% CI 3.66–7.63), and gonorrhea (OR = 5.96, 95% CI 4.15–8.60). Willingness to pay for an STI vaccine was also associated with vaccine interest for syphilis (OR = 2.02, 95% CI 1.29–3.19), chlamydia (OR = 2.41, 95% CI 1.50–3.90), and gonorrhea (OR = 2.29, 95% CI 1.44–3.63). Ever having sexual intercourse and identifying as LGBTQ were significantly associated with vaccine interest for all infections, while age and ever being immunosuppressed were not significant in any adjusted models.

**Conclusion** Findings indicate over 80% of participants in a cohort of young HPV-vaccinated Canadian women are interested in receiving future bacterial STI vaccines. Further exploration of STI vaccine acceptability among diverse populations is required to inform future bacterial STI vaccine program implementation.

## Résumé

**Objectif** Cette étude visait à explorer l'acceptabilité des vaccins contre les ITS bactériennes chez les jeunes Canadiennes vaccinées contre le VPH pour éclairer la mise en œuvre de futurs programmes de vaccination.

**Méthode** Un questionnaire transversal de 20 questions a été administré entre juin 2019 et juin 2020 aux participantes de la cohorte QUEST pancanadienne ayant été vaccinées contre le VPH. Des modèles de régression logistique multivariée ont permis d'analyser l'intérêt pour les vaccins contre la chlamydia, la syphilis et la gonorrhée à l'aide de variables a priori et des facteurs significatifs dans l'analyse bivariée.

**Résultats** Sur les 1 092 répondantes analysées, 82 % ont manifesté l'intérêt de recevoir un ou plusieurs futurs vaccins contre les ITS. L'âge médian des répondantes était de 19,6 ans (intervalle 16,9–23,4), et 75 % s'identifiaient comme étant blanches/

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ORIGINAL ARTICLE

# Kawasaki Disease Arab Initiative [Kawarabi]: Establishment and Results of a Multicenter Survey

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**Abstract**
Studies on Kawasaki disease (KD) in Arab countries are scarce, often providing incomplete data. This along with the benefits of multicenter research collaboratives led to the creation of the KD Arab Initiative [Kawarabi] consortium. An anonymous survey was completed among potential collaborative Arab medical institutions to assess burden of KD in those countries and resources available to physicians. An online 32-item survey was distributed to participating institutions after conducting face validity. One survey per institution was collected. Nineteen physicians from 12 countries completed the survey representing 19 out of 20 institutions (response rate of 95%). Fifteen (79%) institutions referred to the 2017 American Heart Association guidelines when managing a patient with KD. Intravenous immunoglobulin (IVIG) is not readily available at 2 institutions (11%) yet available in the country. In one center (5%), IVIG is imported on-demand. The knowledge and awareness among countries' general population was graded (0 to 10) at median/interquartiles (IQR) 3 (2–5) and at median/IQR 7 (6–8) in the medical community outside their institution. Practice variations in KD management and treatment across Arab countries require solid proactive collaboration. The low awareness and knowledge estimates about KD among the general population contrasted with a high level among the medical community. The Kawarabi collaborative will offer a platform to assess disease burden of KD, among Arab population, decrease practice variation and foster population-based knowledge.

**Keywords** Kawasaki disease · Arab · Multicenter collaborative · Registry · Cardiac complications · Survey

## Introduction

Kawasaki disease (KD) is the most common acquired heart disease in children in most socioeconomically developed countries [1]. The prevalence, clinical findings and cardiac complications are well studied in western countries and Japan [2, 3]. The disease affects children of different ethnicities at different rates due to genetic factors [1, 4, 5]. The clinical findings and cardiac complications have been well described for children with KD in Eastern Asian and in western nations [6]. Data on KD in the Arab countries are limited to case reports and small single-center studies [7, 8]. KD prevalence among Arab descents appears to be higher in North America compared to the countries of origin. In a Canadian multicenter collaborative study of the annual prevalence and complication rates of KD among Arabic community living in the province of Quebec, the prevalence was 4 to 12 times higher than in their countries of origin [9]. The rates of consanguinity in the Arab world are high. Consanguineous marriages constitute 20–50% of all marriages across Arabic countries, including first-cousin unions [10, 11]. This may help understand the genetic factors influencing children affected by KD.

The recent emergence of 2019 coronavirus disease (COVID-19) and the similarity between KD and the Multi-System Inflammatory Syndrome in Children (MIS-C) brought to the stage the importance of studying KD globally [12–20]. Through professional and personal communications among peers in Middle Eastern countries, a growing concern and awareness toward KD was a recurrent theme. A need for a better understanding of each country's KD status led to a collaborative effort to address unanswered questions.

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RESEARCH

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# Oral versus intravenous sildenafil for pulmonary hypertension in neonates: a randomized trial

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## Abstract

**Background:** Sildenafil is the drug of choice for neonatal pulmonary hypertension in developing countries where inhaled nitric oxide is not available. Available as oral and intravenous preparation – no study has been done in the past to compare the two forms. Each has its own benefits – but requires comparison in terms of efficacy and safety. This study was done to compare the efficacy of oral versus intravenous (IV) sildenafil in infants with mild to moderate pulmonary hypertension.

**Methods:** An open labelled randomized trial was conducted in a neonatal intensive care unit of urban tertiary hospital in western India between February 2019 to December 2020. Infants born after 34 weeks of gestation with Pulmonary arterial pressure (PAP) > 25 mm Hg measured by echocardiography, within 72 h of birth, were enrolled for the study. Participants were randomly assigned to receive sildenafil either orally or by intravenous route. Primary outcome was the time taken for PAP to decrease below 25 mm Hg. Secondary outcomes were time taken for oxygenation index to decrease by 25%, duration of invasive and non-invasive mechanical ventilation, nasal oxygen, hospital stay, time to achieve full feeds, mortality, and side effects.

**Results:** Forty patients were enrolled. The baseline characteristics of neonates in both groups were similar except for APGAR scores at 1 min and 5 min, with oral group having lower score [MEDIAN (IQR) 5.00 (4.00- 7.00) and 7.00 (6.00-8.00)] compared to IV group [MEDIAN (IQR) 7.00 (6.00–8.00) and 9.00 (8.00–9.00)] respectively. Time taken for PAP to decrease below 25 mm was not statistically different between the oral and intravenous groups. Systemic hypotension occurred in 4 neonates of the intravenous group but none in the oral group.

**Conclusion:** Oral and intravenous sildenafil had equal efficacy at reducing PAP in neonatal pulmonary hypertension, albeit intravenous sildenafil use was associated with a greater complication rate.

**Trial registration:** Trial was registered in the clinical trials registry of India [CTRI/2019/04/018781][25/04/2019].

**Keywords:** Intravenous sildenafil, Neonates, Oral sildenafil, Pulmonary Hypertension

## Background

Despite new advances in management of persistent pulmonary hypertension of newborn (PPHN), mortality continues to be high, ranging from 4 to 33% [1, 2]. The standard treatment of PPHN in high-income countries, with inhaled nitric oxide (iNO) and extracorporeal membrane oxygenation (ECMO), is expensive and

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RESEARCH Open Access

# Neurodevelopmental outcomes of infants born to mothers with SARS-CoV-2 infections during pregnancy: a national prospective study in Kuwait

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## Abstract

**Background:** An increasing proportion of women are infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during pregnancy. Intrauterine viral infections induce an increase in the levels of proinflammatory cytokines, which inhibit the proliferation of neuronal precursor cells and stimulate oligodendrocyte cell death, leading to abnormal neurodevelopment. Whether a maternal cytokine storm can affect neonatal brain development is unclear. The objective of the present study was to assess neurodevelopmental outcomes in neonates born to mothers with SARS-CoV-2 infections during pregnancy.

**Methods:** In this prospective cohort study, the neurodevelopmental status of infants ($N = 298$) born to women with SARS-CoV-2 infections during pregnancy was assessed at 10–12 months post-discharge using the Ages and Stages Questionnaire, 3rd edition (ASQ-3). The ASQ-3 scores were classified into developmental delays (cutoff scores $\leq 2$ standard deviations (SDs) below the population mean) and no delays (scores $> 2$ SDs above the population mean).

**Results:** The majority (90%) of the infants born to mothers with SARS-CoV-2 infections during pregnancy had favorable outcomes and only 10% showed developmental delays. Two of the 298 infants tested positive for SARS-CoV-2, and both had normal ASQ-3 scores. The majority of the pregnant women had SARS-CoV-2 infections during their third trimester. The risk of developmental delays among infants was higher in those whose mothers had SARS-CoV-2 infections during the first ($P = 0.039$) and second trimesters ($P = 0.001$) than in those whose mothers had SARS-CoV-2 infections during the third trimester.

**Conclusion:** The neurodevelopmental outcomes of infants born to mothers with SARS-CoV-2 infections seem favorable. However, more studies with larger sample sizes and longer follow-up periods are required.

**Keywords:** Coronavirus 2019 (SARS-CoV-2), Pregnancy, Neurodevelopment of infants, Perinatal transmission

## Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), has been spreading rapidly worldwide, increasingly affecting pregnant females. Pregnancy-associated physiological changes, as well as altered cell-mediated

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Rapid Communication

# Effects of BA.1/BA.2 subvariant, vaccination and prior infection on infectiousness of SARS-CoV-2 omicron infections

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**Key words:** COVID-19, Omicron, subvariant, sub-lineage, vaccine, breakthrough infection, immunity, epidemiology

Qatar experienced a large severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron (B.1.1.529) wave that started on 19 December 2021 and peaked in mid-January, 2022.[1] We investigated effects of Omicron subvariant (BA.1 and BA.2), previous vaccination and prior infection on infectiousness of Omicron infections, between 23 December 2021 and 20 February 2022. Incidence was initially dominated by BA.1, but within a few days, BA.2 predominated (Supplementary Figure S1 and Supplementary Section S1, Supplementary Appendix).

The quantitative reverse transcription polymerase chain reaction (RT-qPCR) cycle threshold (Ct) value of a SARS-CoV-2 infection represents the inverse of viral load and is correlated with culturable virus; thus, it can be used as a proxy for SARS-CoV-2 infectiousness.[2,3] Accordingly, a low Ct value implies high infectiousness.

Univariable and multivariable regression analyses were conducted to estimate the association between Ct value and each of the Omicron subvariants, mRNA vaccination (factoring dose number and time since vaccination), prior infection, reason for RT-qPCR testing, calendar week of RT-qPCR testing (to account for phases of the rapidly evolving Omicron wave) and demographic factors including sex, age and nationality (Section

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# Hypernatremia in Newborns: A Practical Approach to Management

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**Keywords**
Neonate · Dehydration · Preterm · Sodium

**Abstract**
Hypernatremia is a potentially serious condition in both term and preterm babies, which can lead to severe and permanent neurological damage. There are many physiological changes in sodium homeostasis that occur soon after birth. Understanding this physiological process, early anticipation of hypernatremia and familiarization with the neonatal management of hypernatremia can prevent mortality and long-term morbidity associated with this condition. This review aims to provide a practical and understandable approach to the diagnosis and management of hypernatremia in neonates.



## Introduction

Hypernatremia, defined as serum sodium of more than 145 mEq/L [1], is a common finding in preterm neonates in the neonatal intensive care unit (NICU) and in term infants after discharge from the hospital. Late recognition and delayed treatment lead to severe and prolonged hypernatremia with an increased risk of mortality and central nervous system morbidities like seizures, thrombosis, intracranial hemorrhage [2–4]. Extracerebral complications include acute kidney injury, transaminitis, hyperglycemia or hypoglycemia, metabolic acidosis, and disseminated intravascular coagulation [5]. Mortality and morbidity are related to hypernatremia itself [6] and inappropriate fluid management [4, 7–9].

The precise incidence of hypernatremia in newborns is difficult to ascertain because of variable incidence based on geographical location, limited accessibility to hospital data, and limited post-discharge follow-up data. However, the reported incidence in term newborns after discharge from the hospital varies from 1% [10] to 1.8% [11] to as high as 5.6% [12]. The main risk factors for hypernatremia in term newborns are related to early discharge from the hospital with ineffective lactation support or insufficient milk production leading to lactation failure [13–16].

In preterm infants, the reported incidence of hypernatremia is about 40% [17] and is usually due to insufficient fluid intake, excessive fluid loss, or excessive sodium intake [18]. Potential etiologies of hypernatremia in preterm and term neonates are summarized in Table 1.

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WPA public health mission to emphasize the importance of risk factors and to adopt evidence-based preventive and rehabilitative interventions.

The WPA Working Group on IDD has participated this year in the initiative called Rehabilitation 2030, sponsored by the WHO Department of Noncommunicable Diseases, Disability, Violence, and Injury Prevention, aiming to develop a package of rehabilitative interventions[7] along with specified resource requirements for their delivery. The overarching goal is the improved care of persons with IDD across the lifespan, with a particular emphasis on LMICs.

Following on these ground-breaking approaches in classification and evidence-based interventions, the Working Group is now promoting a second paradigm shift aiming to include training on IDD within mainstream psychiatry, once again with a particular emphasis on LMICs.

Three important arguments justify this call. First, when polled about their knowledge on the impact of IDD, many trainees in psychiatry recognize the disproportionately high burden of co-occurring mental disorders in persons with IDD[8]. Second, when offered opportunities to interact with persons with IDD during rotations, many trainees in psychiatry regard such experiences as highly formative and inspiring. Third, and most important, psychiatry as a profession has the potential to improve significantly the care for persons with IDD.

Furthermore, the gap in mental health services for persons with IDD is too significant to be compensated by an *ad hoc* reliance on individual providers and families, and their resilience is not limitless. Moreover, within the context of the COVID-19 pandemic, persons with IDD are facing the utmost intensification of inequities in term of underlying medical liabilities, inability to socially distance, increased infection and mortality risks, challenges to participate in telehealth services, and ensuing social isolation and adverse mental health outcomes[9].

The Working Group and the WPA leadership invite Member Societies to work collectively to enhance efforts for the development of inclusive training models in the mental care of persons with IDD. The Working Group is ready to provide awareness raising, training, and research collaboration to promote and disseminate effective services and thereby improve the lives and outcomes for persons with IDD. For this purpose, the Working Group is developing an open access handbook focusing on global aspects of the psychiatry of IDD, with authorship from both LMICs and high-income countries. In parallel, the Working Group is developing online educational materials summarizing the key aspects of psychiatric care in people with IDD. These resources will be accessible through the WPA educational portal in 2022.

The WPA Working Group on IDD encourages systematic exposure to and experience in this area for all psychiatrists, so that they can adjust treatments for co-occurring mental disorders and avoid diagnostic overshadowing in which IDD may be wrongly considered the cause of all behavioural problems, and psychiatric, physical as well as environmental factors may be overlooked. Since relatives remain key partners as well as co-providers of services for people with IDD throughout their lives, the Working Group encourages provision of support to families by using local networks, with access to specialists for training and supervision as well as to more intensive forms of treatment for co-occurring problems (e.g., autism spectrum and seizure disorders)[7]. Third, the Working Group calls for the development of targeted mental health services including psychiatrists and allied professionals, who will need additional training to improve their diagnostic and therapeutic skills relevant to IDD. Finally, the Working Group emphasizes the need for person-centered care tailored on abilities and aspirations of affected persons, blending the social and medical models of development and disability within a human rights framework to improve access to health care, education and employment.

These themes have been the subject of presentations in Presidential and State-of-the-Art Symposia at the World Congress in Lisbon, and subsequently at the World Congresses in Bangkok, Thailand in March 2021, and Cartagena, Colombia in October 2021, and will continue to be addressed by the Working Group at forthcoming WPA congresses and conferences.

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# WPA Working Group on Medical Students: current initiatives and future priorities

Psychiatric issues impact individuals of all ages globally. Shortage of mental health professionals is a major concern especially in low- and middle-income countries. Further, the COVID-19 pandemic has led to downsizing and even closure of various mental health services worldwide[1-4]. In the WPA Action Plan 2020-2023, capacity building and promotion of psychiatry among medical students is an important pillar[5,6]. To this aim, a WPA Working Group on Medical Students has been created. The inau-

gural meeting of this group was held on December 21, 2020, attended by the WPA President. This was followed by regular meetings.

The remit of this Working Group includes four components: to identify opportunities for promoting psychiatry as a career among medical students; to identify organizations and individuals interested in participating and promoting WPA's Action Plan in nurturing psychiatry among medical students; to liaise with other WPA Working Groups regarding medical students; and to support medical students around the world.

Since the beginning of 2019, COVID-19 has caused significant disruptions in the day-to-day lives of millions of people around the world. Medical education is not an exception in this regard. The pandemic has impacted on in-person learning, medical school examinations, clinical rotations, faculty availability for supervision and future placements[7].

The pandemic has also impacted on the emotional well-being of medical students. A study done by members of our Working Group among 1,100 medical students from five medical schools in Pakistan found high rates of anxiety (48.6%) and depressive symptoms (48.1%) during the COVID-19 pandemic. The study included 69% female and 31% male medical students, with approximately 25% reporting past psychiatric issues. One of the most concerning observations was that one in five medical students thought that it would be better if they were dead and 8% often thought about suicide during the past 2 weeks[8]. It is imperative that medical schools develop strategies and support systems to maintain medical student well-being.

A major highlight of the activity of our Working Group has been the release of a promotional video for medical students entitled *Why Psychiatry*. This video was created to share perspectives from seasoned faculty, psychiatry trainees and medical students on the importance of supporting the psychiatry workforce around the world. Interviews included key themes encompassing medical student mental health, the diversity of psychiatric subspecialties, the interface of mental health with social determinants of health, and opportunities to partner with primary care providers. A consistent message was the critical shortage of psychiatrists and the need to support workforce development to address mental health needs. This video is available in English, French, Spanish and Russian for medical educators to share with their trainees and medical students (www.wpanet.org/post/why-psychiatry-medical-student-group-video-now-available-online).

In addition to the video, the Working Group is developing a set of online tools for psychiatric educators. The first of these tools is an interactive self-learning module on the well-being of medical students, which is now available on the WPA educational portal. Self-care and wellness are often ignored in the formal medical school curricula[9]. The current pandemic has increased the visibility of burnout and depression in the health care workforce. This module plans to encourage educators and policy makers to implement student wellness policies and to support a learning environment which nurtures emotional and physical well-being.

In order to augment the virtual resources, the Working Group has organized three in-person events to promote psychiatry among medical students and address burnout. These inaugural events were held in Pakistan, India and Qatar, with active participation from local medical students, who provided input on core topics. These events also served as a platform to support and mentor medical students interested in psychiatry.

The Working Group is active in publishing peer-reviewed articles, covering areas such as promoting psychiatry among medical students and the impact of COVID-19 on medical students[10,11]. Additional research articles are planned and underway. All of the activities and initiatives of the Working Group are accessible on the dedicated section of the WPA website (www.wpanet.org/wg-on-medicalstudents).

The Working Group has been active in presenting invited and peer-reviewed abstracts and symposia around the world. This included presidential and other symposia on psychiatry capacity building and medical education themes at the World Congresses in Bangkok, Thailand in March 2021, and Cartagena, Colombia in October 2021. Abstracts on the promotion of psychiatry were presented at the annual conferences of the Association of University Teachers of Psychiatry Annual Conference, UK in February 2021; at the WPA Regional Conference, Russia in May 2021; and at the 67th Virtual American Academy of Child and Adolescent Psychiatry Conference in October 2021. An innovative contest was held among medical students in Mexico to submit papers on "The Role of Psychiatry after the Pandemic". The top three papers were recognized during the 27th Congress of the Mexican Psychiatric Association in September 2021.

Future directions include: a) to create online self-learning modules on "stigma" and "burnout" for medical students; b) to conduct a survey about psychiatry curriculum in medical education across medical schools in different countries; c) virtual and in-person activities to promote psychiatry among medical students and to address burnout among students; d) to liaison with regional and international organizations to promote psychiatry; e) presentations at the WPA congresses and other national and international conferences; and f) social media and video campaigns to promote psychiatry.

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# WPA Working Group on Public Mental Health: objectives and recommended actions

Mental disorder is reported to account for almost a third of global disease burden as measured by years lived with disability (YLDs)[1]. On the other hand, mental well-being results in broad positive impacts[2]. Effective public mental health interventions exist to treat mental disorder, prevent associated impacts, prevent mental disorder from arising, and promote mental well-being and resilience[2,3].

However, only a minority of those with mental disorder receive treatment, with far lower coverage in low- and middle-income countries (LMICs)[4]. There is even less coverage of interventions to prevent associated impacts of mental disorder, and negligible coverage of interventions to prevent mental disorder, or promote mental well-being and resilience. This implementation gap represents a breach of the right to health, and results in population-scale suffering and associated economic costs[3]. The gap has further widened during the COVID-19 pandemic[5-7].

The United Nations (UN) Sustainable Developmental Goals have set a target of universal coverage by 2030 which includes treatment and prevention of mental disorder and promotion of mental well-being. The most recent World Health Organization (WHO) Mental Health Atlas highlighted that "global targets can be reached in 2030 only if there is a collective global commitment over the next 10 years across Member States to make massive investments and expanded efforts at the country level relating to mental health policies, laws, programmes and services"[4].

Public mental health involves a population approach to improve coverage, outcomes and coordination of interventions to treat mental disorder, prevent associated impacts, prevent mental disorder from arising, and promote mental well-being and resilience. This aims to support efficient, equitable and sustainable reduction in mental disorder, promotion of population mental well-being, and achievement of the UN Sustainable Developmental Goals target of universal coverage by 2030[3].

The WPA Action Plan 2020-2023 promotes public mental health as a guiding principle[8,9]. A Working Group on Public Mental Health has been then established, including experts such as J. Allan, F.K. Baingana, J. Campion, Y. Huang, A. Javed, N. Lamb, S. Levin, C. Lund, M. Marmot, S. Saxena, T. Schulze, E. Sorel, H. Tu, P. Udomratn, and M. van Ommeren (observer).

The Working Group highlighted that public mental health is not well defined or understood, with some languages having no terms for it. This contributes to lack of action on relevant issues. The Group agreed upon the definition outlined above, which is reported on the Group webpage of the WPA website (www.wpanet.org/public-mental-health) and in a recent publication[3].

The main objective of the Working Group is to improve implementation of public mental health interventions in four ways. The first is to raise awareness, value, acceptance and prioritization of this area in national health policies. The second is to promote national assessments of public mental health unmet need and required actions which can then inform policy development and implementation. The third is to promote public mental health training, including through digital platforms, which can support psychiatrists and other professionals to address the public mental health implementation gap, particularly in LMICs, through identification of required actions by different sectors as well as clarification of a core curriculum, training targets and milestones. Examples of public mental health training are highlighted on the above-mentioned Group webpage. The fourth way is to support development of integrated public mental health approaches to disease management and prevention including through engagement with primary and general health systems.

Further objectives include: a) work with interested countries in order to facilitate these approaches with identified funding; b) engagement with other organizations on the public mental health agenda – thus far, these have included the Organization for Economic Co-operation and Development (OECD), the UN International Children's Emergency Fund (UNICEF), and the WHO; c) disseminating work relevant to public mental health through publications, presentations and training, also delivered online; d) supporting a public mental health approach in other areas of the WPA Action Plan 2020-2023, including child, adolescent and youth mental health, the management of comorbidities, and partnership with other organizations.

Publications already produced by the Working Group include an editorial on the field as a whole[10], articles dealing with the public mental health approach to the COVID-19 pandemic[11-13], and papers about required actions to address public mental health implementation failure[3,14]. Members of the Working Group have given and will give presentations at World Congresses of Psychiatry in 2021 and 2022, and will present in a public mental health symposium at the 2022 International Congress of the UK Royal College of Psychiatrists.

In order to achieve consensus on required actions to address the public mental health implementation gap, the members of the Working Group were invited to contribute to a health policy article[3], which recommends the following six actions: a) making the public mental health case through assessment of unmet need, estimation of impact and associated economic benefits from improved coverage, as well as collabo-

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ESPR

# Imaging of anorectal malformations: where are we now? Abdominal imaging task force of the European Society of Paediatric Radiology

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**Abstract**
Anorectal and cloacal malformations are a broad mix of congenital abnormalities related to the distal rectum and anus. Confusion exists between all the forms in this large and heterogeneous group. The spectrum includes everything from anal stenosis, ventral anus, anal atresia (with and without fistula) and the full spectrum of cloacal malformations. Imaging in these conditions is done through the whole armamentarium of radiologic modalities, with very different imaging strategies seen across the centres where these conditions are managed. In 2017, the European Society of Paediatric Radiology (ESPR) abdominal imaging task force issued recommendations on the imaging algorithm and standards for imaging anorectal malformations. This was followed by further letters and clarifications together with an active multispecialty session on the different imaging modalities for anorectal malformations at the 2018 ESPR meeting in Berlin. Through this paper, the abdominal task force updates its guidelines and recommended imaging algorithm for anorectal malformations.

**Keywords** Anorectal malformation · Anus · Children · Cloacal malformation · Fluoroscopy · Infants · Magnetic resonance imaging · Radiography · Rectum · Ultrasound

## Introduction

Anorectal and cloacal malformations are a broad mix of congenital abnormalities related to the distal rectum and anus. There is a male predominance with a prevalence of around 1:5,000 [1] for anorectal malformations (ARMs), whereas cloacal malformations are much more uncommon (1:50,000) and seen almost exclusively in girls. Cloacal malformation represents a common perineal outflow tract of the urinary tract, vagina and rectum.

Although considered the most serious form of ARMs, cloacal malformations represent a further broad spectrum of conditions with multiple associations (specific anomalies and syndromes) with respective imaging and treatment implications.

Confusion exists between all the forms in this large and heterogeneous group. The spectrum includes everything from anal stenosis, ventral anus, anal atresia (with and without fistula) and the full spectrum of cloacal malformations (Fig. 1).

There is a high incidence of associated congenital anomalies with ARM (Table 1).

Imaging in these conditions is done through the whole armamentarium of radiologic modalities with very different imaging strategies seen across the centres where these conditions are managed.

Correct identification and diagnosis have significant surgical and outcome implications – the management targets being long-term continence and good quality of life.

## Classifications

The accepted classification for ARMs is now the clinically oriented Krickenbeck classification (Table 2) established in 2005 [2, 3]. Considerations that better inform surgical decisions include:

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nature COMMUNICATIONS

ARTICLE

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# Duration of mRNA vaccine protection against SARS-CoV-2 Omicron BA.1 and BA.2 subvariants in Qatar

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SARS-CoV-2 Omicron BA.1 and BA.2 subvariants are genetically divergent. We conducted a matched, test-negative, case-control study to estimate duration of protection of the second and third/booster doses of mRNA COVID-19 vaccines against BA.1 and BA.2 infections in Qatar. BNT162b2 effectiveness was highest at 46.6% (95% CI: 33.4–57.2%) against symptomatic BA.1 and at 51.7% (95% CI: 43.2–58.9%) against symptomatic BA.2 infections in the first three months after the second dose, but declined to ~10% or below thereafter. Effectiveness rebounded to 59.9% (95% CI: 51.2–67.0%) and 43.7% (95% CI: 36.5–50.0%), respectively, in the first month after the booster dose, before declining again. Effectiveness against COVID-19 hospitalization and death was 70–80% after the second dose and >90% after the booster dose. mRNA-1273 vaccine protection showed similar patterns. mRNA vaccines provide comparable, moderate, and short-lived protection against symptomatic BA.1 and BA.2 Omicron infections, but strong and durable protection against COVID-19 hospitalization and death.

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# Left Ventricular Dysfunction Persists in the First Week after Re-Warming following Therapeutic Hypothermia for Hypoxic-Ischaemic Encephalopathy

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**Keywords**
Hypoxic-ischaemic encephalopathy · Therapeutic hypothermia · Tissue Doppler imaging

**Abstract**
***Objectives:*** The aim of this study was to assess serial myocardial function in newborn infants receiving therapeutic hypothermia (TH) as treatment for moderate to severe hypoxic-ischaemic encephalopathy (HIE). ***Methods:*** Serial echocardiography was performed in 20 term infants receiving TH on days 1–3 and again after re-warming. Left ventricular (LV) fractional shortening, LV cardiac output, and tissue Doppler imaging-derived myocardial velocities and myocardial performance index were measured. Similar assessments were obtained from 20 well term infants within 48 h of birth. ***Results:*** LV fractional shortening (LVFS) was similar between cases and controls during all measurements (25.3% vs. 27.4%). The mean LV cardiac output on day 1 was significantly lower in cases (109 mL/kg/min) than in controls (162 mL/kg/min) but increased after re-warming (145 mL/kg/min). All myocardial velocities were significantly lower in cases on day 1, increased during TH, but LV indices remained consistently lower compared to controls even after re-warming. LV myocardial performance index was higher in cases compared to controls on day 1, improved during TH but remained abnormal after re-warming. The right ventricular myocardial performance index was similar between cases and controls. ***Conclusion:*** Among infants affected by moderate to severe HIE, LV function appears to be more affected than right ventricular function with LV dysfunction persisting after completion of TH. LVFS was not useful to determine dysfunction in this cohort.



## Introduction

Hypoxic-ischaemic encephalopathy (HIE) following a perinatal asphyxial insult in term babies is a multisystem disorder resulting in death or severe neurological injury.

Dr. Shree Vishna Rasiah has unfortunately died after this study was completed.

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# The role of bedside functional echocardiography in the assessment and management of pulmonary hypertension

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*Keywords:*
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ABSTRACT

Pulmonary hypertension is an emergency in neonatal intensive care units with high morbidity and mortality. Its timely assessment and management is crucial for intact survival. Over the last couple of decades, there have been significant advances in management and techniques, which have resulted in improved survival. The use of neonatologist-performed echocardiography (NPE) is now increasingly utilized on neonatal intensive care units to understand the pathophysiology of the disease and to direct the treatment to the underlying cause. Its use is now established not only in cases of congenital diaphragmatic hernia and in the newborn with refractory hypoxemia, but also in other conditions such as bronchopulmonary dysplasia and the premature infant with difficulty in oxygenation. The use of NPE, however, requires the availability of trained personnel, equipment, and a close working relationship with pediatric cardiology.

## 1. Background

Pulmonary hypertension (PH) of the newborn is characterized by increased pulmonary vascular resistance with pulmonary-to-systemic shunting of deoxygenated blood resulting in severe hypoxemic respiratory failure (HRF) [1]. Broadly, PH can be classified under three categories - abnormally constricted pulmonary vasculature secondary to parenchymal diseases (maladaptation), hypoplastic pulmonary vasculature (underdevelopment) and normal parenchyma with remodelled pulmonary vasculature (maldevelopment) with various conditions contributing to it (Table 1). The commonest cause of PH in the newborn period is persistent pulmonary hypertension of the newborn (PPHN), which is erroneously also called persistent fetal circulation [PFC], which occurs from a failure of the lung circulation to achieve or sustain the normal drop in pulmonary vascular resistance (PVR) at birth [2,3]. PPHN affects 0.2% of all live births and is a significant contributor to the mortality and morbidity in term and late preterm infants.

PPHN results in impaired oxygenation, right ventricular failure, and pulmonary-to-systemic shunting. In the premature infant, where the pulmonary vasculature is either maladapted, maldeveloped, or underdeveloped, the mechanisms are similar, and the pulmonary hypertension is usually secondary to pulmonary vascular immaturity. The incidence of acute PH in preterm infants is not clearly defined, but its prevalence could be higher than in term infants, as the lung parenchymal disease is more common because of immaturity of the lung [4]. Late-onset pulmonary hypertension, on the other hand, results from maldevelopment of the pulmonary circulation and is seen with severe bronchopulmonary dysplasia (BPD). The prevalence of PH in infants with severe BPD is under recognised with higher mortality compared to those without BPD [5].

NPE or bedside/point of care functional echocardiography (fECHO) has gained recent global interest. It has become an integral part of neonatal practice in many centers [6,7]. Guidance on assessment and management of PH by NPE has been published [8]. When there is a clinical suspicion of PPHN and structural heart disease has been ruled out, fECHO assessment is recommended. NPE is an important tool for confirming the diagnosis and grading of PPHN, objective selection of specific therapies, and titrating and monitoring response to treatment. Specific protocols are available for assessing PH related to bronchopulmonary dysplasia [9,10], late onset sepsis [11], and congenital diaphragmatic hernia [12,13]. The aim of this article is to provide guidance to neonatologists undertaking fECHO examinations of newborn infants

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# Diabetic ketoacidosis fluid management in children: systematic review and meta-analyses

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## ABSTRACT

**Importance** Diabetic ketoacidosis (DKA) is a serious complication of type 1 diabetes mellitus, which may lead to significant morbidity and mortality.

**Objectives** To compare the safety and efficacy of liberalised versus conservative intravenous fluid regimens in the management of DKA in children.

**Data source and study selection** Databases from inception to January 2022: MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials were included. Only randomised controlled trials (RCTs) that included children aged under 18 years were assessed. Two reviewers performed data assessment and extraction.

**Data extraction and synthesis** Three studies out of 1536 citations were included.

**Main outcomes** The time to the recovery from the DKA; the frequency of paeditric intensive care unit (PICU) admissions; development of brain oedema; reduction in Glasgow Coma Scale (GCS); development of acute kidney injury and all-cause mortality.

**Results** We included three RCTs (n=1457). No evidence of difference was noted in the GCS reduction (risk ratio (RR)=0.77, 95% CI 0.44 to 1.36) or development of brain oedema (RR=0.50, 95% CI 0.15 to 1.68). The time to recovery from DKA was longer in the conservative group (mean difference=1.42, 95% CI 0.28 to 2.56). Time to hospital discharge, adverse or serious adverse events were comparable in the two studied groups.

**Conclusion** There is no evidence from this meta-analysis that rate of fluid administration has any effect on adverse neurological and other outcomes or length of hospital stay.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Intravenous fluid and insulin infusions remain the main treatment of diabetic ketoacidosis (DKA). There is no universal agreement on which intravenous fluid regimens should be used (liberalised or conservative).

### WHAT THIS STUDY ADDS

⇒ This review showed that liberalised intravenous fluid is comparable with conservative intravenous fluid administration for management of DKA.

⇒ There is a suggestion that time to recovery from DKA may be slightly longer with conservative intravenous fluid management.

## INTRODUCTION

Diabetic ketoacidosis (DKA) is the leading cause of morbidity and mortality in children and adolescents with type 1 diabetes mellitus (DM).[1] It is a complicated metabolic state, hallmarked by dehydration, hyperglycaemia, hyperosmolarity, acidosis and significant electrolyte disturbances.[2] Between 15% and 67% of children newly diagnosed with type 1 DM present in DKA.[3] The biochemical criteria for the diagnosis of DKA are well defined.[4] The severity of DKA is classified as mild (venous pH <7.30), moderate (pH <7.2) or severe (pH <7.1).[5] The mortality associated with DKA is related to the occurrence of cerebral oedema, only a minority of deaths in DKA are attributed to other causes. Cerebral injury occurs in 0.3%–0.9% of children with DKA and has a mortality rate of 21%–24%.[6–8] Despite many efforts to identify the cause of cerebral oedema, its pathogenesis is not completely understood and controversy continues regarding the association between the rate of intravenous fluid or sodium administration used in the treatment of DKA and the development of cerebral oedema.[9–11]

The aim of this systematic review was to assess the safety and efficacy of liberalised versus conservative intravenous fluid regimens in treatment of DKA in children. The fluid volume rates are classified according to the main papers identified in this systematic review as liberalised (fast) or conservative (slow), and the exact details are in table 1.

## MATERIALS AND METHODS

### Study selection and search study

We searched the following databases from inception to 19 January 2022: MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials. We inspected reference lists from retrieved articles to identify any additional citations that may have been missed by the electronic searches. Moreover, we searched unpublished ongoing clinical trials on the following websites: www.clinicaltrials.gov and www.controlled-trials.com.

### Search strategy

We included terms for population, interventions and outcomes in our search strategy. Search terms used: diabetic ketoacidosis OR [DKA] AND [fluids OR intravenous fluids OR rehydration] AND [children or paediatric].

Check for updates



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# A Conceptual Framework for Fetus Head Analysis Based on Ultrasound Images

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**Abstract.** Ultrasound images are the most used imaging methodologies in obstetrics to monitor the growth of a fetus during the gestation period. In particular, the obstetrician uses fetus head images to monitor the growth state and identify essential features such as Gestational age (GA), estimated fetus weight (EFW), and brain anatomical structures. However, this work requires an expert obstetrician, and it is time-consuming and costly. Therefore, we proposed an automatic framework by adopting a hybrid approach that combines three components i) automatic segmentation to segment the region of interest (ROI) in the fetus head, ii) measurement extraction to measure the segmented ROI, and iii) anomaly and features detection to predict fetus GA, EFW, and abnormality status.

**Keywords.** Image segmentation, fetus head, Gestational age, Estimated fetus weight, fetus abnormality, Ultrasound

## 1. Introduction

Ultrasonic imaging, abbreviated as ultrasound, is extensively used in clinical assessment because it does not use ionizing radiation and is less expensive than computed tomography (CT) and magnetic resonance imaging (MRI), respectively [1]. During pregnancy, women typically have one to three ultrasounds; however, if the woman is pregnant with twins, ultrasounds may be required more regularly [2].Ultrasound is used in a variety of prenatal diagnostic situations, including confirming pregnancy and fetus position, calculating the gestational age of the fetus, verifying the number of fetuses, examining fetus development, determining the amount of placenta and amniotic fluid, identifying congenital disabilities, and investigating complications, among others [3]. When ultrasonography is used routinely throughout early pregnancy, it results in earlier detection of issues and improved management of pregnancy difficulties, as opposed to depending on clinical signs such as bleeding during early pregnancy [4].

Many clinical ultrasonography diagnostics necessitate the use of anatomical structure measurements that are clear and reliable. These measurements are essential to monitoring fetus growth patterns during pregnancy. [5]. For instance, Crown-rump length (CRL), HC (head circumference), and biparietal diameter (BPD) are required to estimate fetus gestational age (GA) [6]. Further, abdominal circumference (AC), Femur

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life

MDPI

*Review*

# Role of Obesity in Inflammation and Remodeling of Asthmatic Airway

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**Abstract:** Obesity is considered as an important risk factor for the onset of asthma and plays a key role in enhancing the disease's severity. Obese asthmatic individuals represent a distinct phenotype of asthma that is associated with additional symptoms, more severe exacerbation, decreased response to standard medication, and poor quality of life. Obesity impairs the function of the lung airway in asthmatic individuals, leading to increased inflammation and severe remodeling of the bronchus; however, the molecular events that trigger such changes are not completely understood. In this manuscript, we review the current findings from studies that focused on understanding the role of obesity in modulating the functions of airway cells, including lung immune cells, epithelial cells, smooth muscle cells, and fibroblasts, leading to airway inflammation and remodeling. Finally, the review sheds light on the current knowledge of different therapeutic approaches for treating obese asthmatic individuals. Given the fact that the prevalence of asthma and obesity has been increasing rapidly in recent years, it is necessary to understand the molecular mechanisms that play a role in the disease pathophysiology of obese asthmatic individuals for developing novel therapies.

**Keywords:** obesity; asthma; inflammation; airway remodeling; airway epithelial cells; airway smooth muscle cells; lung fibroblasts



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## 1. Introduction

Asthma is a major non-communicable disease that affects both the pediatric and adult populations worldwide. Asthma's prevalence has been increasing significantly worldwide in recent years. A global study recently reported that approximately 300 million people are affected by asthma worldwide, and around 1000 people die from asthma every day [1]. Clinically, asthma is considered as a chronic lung disease associated with airway limitation due to a combination of pathophysiological events, including hypersensitivity, the inflammation and remodeling of the airway, and hypersecretion of the mucus leading to reduced airway function [2]. Obesity is considered as a major health problem. Extensive epidemiological studies have established a strong link between asthma and obesity, and indicated that obesity can serve as a major predisposing factor for asthma onset in children and adults (Table 1), [3–6]. A meta-analysis using different prospective pediatric cohort studies discovered a dose–response association between asthma and body weight, and revealed that overweightness and obesity increase the asthma risk by 20% and two-fold, respectively, in children [7]. As compared with all other asthma phenotypes, obese asthmatic patients are associated with additional symptoms, poor disease control, a higher rate of exacerbation, attenuated response to corticosteroid treatment, and reduced quality of life. Furthermore, most of the asthmatic patients that fall under the difficult-to-treat category are found to be obese [8,9].

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# Antenatal Magnesium Sulfate for Preterm Neuroprotection: A Single-Center Experience from Kuwait Tertiary NICU

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**Keywords**
Preterm · Magnesium sulfate · Newborn infant · Neuroprotection

**Abstract**

***Objectives:*** The study aimed to evaluate the impact of antenatal exposure of magnesium sulfate ($MgSO_4$) on short- and long-term outcomes in preterm neonates born less than 32 weeks gestation. ***Methods:*** Single-center retrospective cohort study of 229 neonates born between 24 and 32 weeks gestation was conducted from January 2018 through December 2018 in a level III neonatal care unit in Kuwait. Antenatal $MgSO_4$ exposure was collected from the medical records, and the indication was for neuroprotection effect. Brain MRI was done on 212 neonates (median gestational age 36 weeks), and brain injury was assessed using the Miller's score. Neurodevelopmental outcome was assessed by Bayley-III scales of infant development at 36 months corrected age ($N = 146$). The association of exposure to MgSO4 with brain injury and neurodevelopmental outcomes was examined using multivariable regression analysis adjusting for gestational age at MRI and variables with $p$ value <0.05 on univariate analysis. ***Results:*** Among the 229 neonates, 47 received antenatal $MgSO_4$. There were no differences between the groups in gestational age and birth weight. $MgSO_4$ exposure was not associated with an increased risk of necrotizing enterocolitis, chronic lung disease, retinopathy of prematurity, and mortality. The incidence of cerebellar hemorrhage was significantly less in the $MgSO_4$ group (0% vs. 16%, $p$ value = 0.002). Neonates who received $MgSO_4$ had lower risks of grade 3–4 intraventricular hemorrhage (IVH) adjusted OR 0.248 (95% CI: 0.092, 0.66), $p = 0.006$; moderate-severe white matter injury (WMI) adjusted odd ratio 0.208 (95% CI: 0.044, 0.96), $p = 0.046$; and grade 3–4 IVH and/or moderate-severe WMI adjusted OR 0.23 (95% CI: 0.06, 0.84), $p = 0.027$. Neurodevelopmental assessment at 36 months corrected age showed better motor (adjusted beta coefficient 1.08 [95% CI: 0.099, 2.06]; $p = 0.031$) and cognitive composite scores (adjusted beta coefficient 1.29 [95% CI: 0.36, 2.22]; $p = 0.007$) in the $MgSO_4$ group. ***Conclusion:*** Antenatal exposure to $MgSO_4$ in preterm neonates less than 32 weeks was independently associated with lower risks of brain injury and better motor and cognitive outcomes.



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# Landscape of childhood epilepsies – A multi-ethnic population-based study

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ABSTRACT

*Objective:* To describe the clinical features of childhood epilepsy in Qatar.
*Methods:* A retrospective cross-sectional chart review analysis was conducted at the only tertiary pediatric hospital in Qatar in 1422 patients with epilepsy followed between November 2016 and October 2019.
*Results:* 55% (781) were males and 70% were non-Qatari. Age of epilepsy onset was in the neonatal period in 9% (114/1207 patients). In the non-neonatal cohort, mean age of onset was 4 yrs 9mos ( ± 1.4mos). Focal epilepsy was the predominant epilepsy type in 45% (594/1314 patients) versus generalized epilepsy in 37% and combined focal/generalized epilepsy in 12%. Etiology was unknown in most children (782/1363, 57%) whereas structural and genetic causes represented 23% and 11% of cases respectively. No differences in epilepsy type and etiology were found between different ethnic groups. Children with genetic or structural epilepsies had an earlier epilepsy onset compared to those with unknown etiologies. At the last follow up, only 36% of patients were seizure-free and 12% (170/1422) had a history of status epilepticus. Medically refractory epilepsy was found in 37% (527/1407) of patients, with the most common etiologies being unknown (36%) and structural (37%). Neurodevelopmental co-morbidities were present in most patients (62%), with global developmental delay (47%) and learning/school difficulties (22%) being the most prevalent. 94% of patients with somatic co-morbidities had concomitant neurodevelopmental co-morbidities. Risk factors associated with an increased risk of co-morbidities and intractable epilepsy included early age of epilepsy onset (< 2 years of age); etiology; antenatal risk factors; history of previous central nervous system infection; history of status epilepticus and a family history of consanguinity and epilepsy.
*Significance:* This large multi-ethnic population-based study confirms that the prevalence, incidence and clinical features of epilepsy in Qatar is in accordance with other epidemiologic studies and highlights risk factors for the development of co-morbidities and medically-intractable epilepsy.

## 1. Introduction

Epilepsy is a common pediatric neurologic condition, defined as "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition" (Fisher et al., 2005). Most patients with epilepsy begin to manifest with seizures in childhood, with the worldwide incidence estimated at 41–187/100,000 (Camfield and Camfield, 2015; Shinnar and Pellock, 2002). Causes of epilepsy in children are diverse and vary from acquired brain injury (perinatal asphyxia, trauma, infections, stroke, brain tumors) to inherited etiologies (brain malformations, neurogenetic syndromes, channelopathies). In a considerable proportion of patients however, the cause of the epilepsy remains unknown (Camfield and Camfield, 2015; Wirrell et al., 2011).

Various epidemiologic studies have demonstrated that in many cases, the prognosis in childhood epilepsies is good, with up to 70–80% of children having their seizures well controlled with antiseizure medications (ASMs) and eventually attaining remission (Berg and Shinnar, 1994; Geerts et al., 2010). Despite this, up to 30% of children with childhood epilepsies have a more severe course characterized by medically intractable seizures and significant medical and psychosocial co-morbidities leading to a diminished quality of life (Ferro, 2014).

Behavioral and neurocognitive deficits are among the most important co-morbidities and are seen in up to 35–50% of children with epilepsy, with rates higher than 50% in children with intractable epilepsy

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ORIGINAL ARTICLE

# Effects of Previous Infection and Vaccination on Symptomatic Omicron Infections

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## ABSTRACT

### BACKGROUND

The protection conferred by natural immunity, vaccination, and both against symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with the BA.1 or BA.2 sublineages of the omicron (B.1.1.529) variant is unclear.

### METHODS

We conducted a national, matched, test-negative, case–control study in Qatar from December 23, 2021, through February 21, 2022, to evaluate the effectiveness of vaccination with BNT162b2 (Pfizer–BioNTech) or mRNA-1273 (Moderna), natural immunity due to previous infection with variants other than omicron, and hybrid immunity (previous infection and vaccination) against symptomatic omicron infection and against severe, critical, or fatal coronavirus disease 2019 (Covid-19).

### RESULTS

The effectiveness of previous infection alone against symptomatic BA.2 infection was 46.1% (95% confidence interval [CI], 39.5 to 51.9). The effectiveness of vaccination with two doses of BNT162b2 and no previous infection was negligible (–1.1%; 95% CI, –7.1 to 4.6), but nearly all persons had received their second dose more than 6 months earlier. The effectiveness of three doses of BNT162b2 and no previous infection was 52.2% (95% CI, 48.1 to 55.9). The effectiveness of previous infection and two doses of BNT162b2 was 55.1% (95% CI, 50.9 to 58.9), and the effectiveness of previous infection and three doses of BNT162b2 was 77.3% (95% CI, 72.4 to 81.4). Previous infection alone, BNT162b2 vaccination alone, and hybrid immunity all showed strong effectiveness (>70%) against severe, critical, or fatal Covid-19 due to BA.2 infection. Similar results were observed in analyses of effectiveness against BA.1 infection and of vaccination with mRNA-1273.

### CONCLUSIONS

No discernable differences in protection against symptomatic BA.1 and BA.2 infection were seen with previous infection, vaccination, and hybrid immunity. Vaccination enhanced protection among persons who had had a previous infection. Hybrid immunity resulting from previous infection and recent booster vaccination conferred the strongest protection. (Funded by Weill Cornell Medicine–Qatar and others.)

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RESEARCH THEME 1: COVID-19 PANDEMIC



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# COVID-19 disease severity in persons infected with the Omicron variant compared with the Delta variant in Qatar

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**Background** Understanding the disease severity associated with the Omicron variant of the SARS-CoV-2 virus is important in determining appropriate management strategies at the individual and population levels. We determined the severity of SARS-CoV-2 infection in persons infected with the Omicron vs the Delta variant.

**Methods** We identified individuals with SARS-CoV-2 infection with Delta and propensity-score matched controls with Omicron variant infection from the National COVID-19 Database in Qatar. We excluded temporary visitors to Qatar, those with a prior documented infection, those ≤18 years old, and those with <14 days of follow up after the index test positive date. We determined the rates of admission to the hospital, admission to intensive care unit, mechanical ventilation, or death among those infected with the Delta or Omicron variants.

**Results** Among 9763 cases infected with the Delta variant and 11 310 cases infected with the Omicron variant, we identified 3926 propensity-score matched pairs. Among 3926 Delta infected, 3259 (83.0%) had mild, 633 (16.1%) had moderate and 34 (0.9%) had severe/critical disease. Among 3926 Omicron infected, 3866 (98.5%) had mild, 59 (1.5%) had moderate, and only 1 had severe/critical disease (overall $P<0.001$). Factors associated with less moderate or severe/critical disease included infection with Omicron variant (aOR=0.06; confidence interval (CI)=0.05-0.09) and vaccination including a booster (aOR=0.30; 95% CI=0.09-0.99).

**Conclusions** Omicron variant infection is associated with significantly lower severity of disease compared with the Delta variant. Vaccination continues to offer strong protection against severe/critical disease.

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The SARS-CoV-2 pandemic has rapidly evolved over time with new viral strains appearing at regular and frequent intervals. The new strains which are associated with significant changes in the behavior of the virus, and/or its effect on the host have been termed "variants of concern" (VOC) and labeled with the Greek alphabets sequentially by the World Health Organization. The Omicron variant is the most recent VOC, which was first identified in South Africa in November 2021, but rapidly spread across the globe and is now the predominant circulating variant in most countries [1-3]. Most Omicron variant infections occur in previously vaccinated per-

PLOS ONE

RESEARCH ARTICLE

# Sib-pair subgroup familial type 1 diabetes mellitus in children in the state of Qatar

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**Data Availability Statement:** Datasets generated in this study are not publicly available but can be obtained from corresponding author on reasonable request. The data set reported in this study is not allowed to be uploaded publicly as it contains patient-level data and it is not allowed to upload the genetic data of citizens of Qatar publicly as per the restrictions imposed by the Ethical Committee. Data access requests may be sent to The Institutional Review Board, Sidra Medicine, Doha-

## Abstract

### Background

Type 1 diabetes is the most common type of diabetes mellitus (DM) in children. It can be sporadic in onset or cluster in families, which comprises parent-offspring and sib-pair subgroups. The risk of developing DM in first-degree relatives of affected individuals is 8–15 fold higher. There is limited data about familial DM from the Gulf region. This study aims to describe the clinical, biochemical and genetic characteristics of sib-pair familial type 1 diabetes in Qatar.

### Methods

Every child with DM following up at Sidra Medicine was recruited. Data was collected regarding clinical features, family history, type 1 diabetes autoantibodies and whole genome sequencing was performed. Genetic analysis for MODY genes and HLA association analysis was conducted.

### Results

44 families with sib-pair familial diabetes were identified. Of these, 2 families had 4 affected siblings and 5 families had 3 affected siblings. The majority are of Qatari ethnicity and the most common autoantibody was GAD65. The most common age of onset in the proband was 5–9 years while it was 10–14 years in subsequent siblings. The occurrence of DKA & HbA1c levels were lower in the second affected sibling. No relevant MODY gene variants were found. HLA analysis found 15 variants in at least 50% of the subjects. Most common were HLA-F*01*01*01G, HLA- DPA1*01*03*01G, HLA- DRB3*02*02*01G, HLA-E*01*01*01G & DRB4*03*01N.

### Conclusions

The prevalence of sib-pair diabetes is 3.64%. The second affected siblings were older. MODY is unlikely and Class I and II HLA genes was present in sib-pair diabetes.

PLOS ONE

RESEARCH ARTICLE

# Aerobiological monitoring in a desert type ecosystem: Two sampling stations of two cities (2017–2020) in Qatar

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**Data Availability Statement:** All relevant data are within the paper. All datasets used or analyzed in this study are present in the paper in their raw form.

## Abstract

### Background

The increasing number of aerobiological stations empower comparative studies to determine the relationship between pollen concentrations in different localities and the appropriate distance, which should be established between sampling stations. In Qatar, this is basically the first aerobiological study for a continuous monitoring interval.

### Objectives

The study aimed to assess the abundance and seasonality of the most prevalent pollen types, plus identify potential differences between two sites within the country.

### Methods

Airborne pollen data were collected during 2017–2020 by using Hirst-type volumetric samplers in Doha capital city and Al Khor city in Qatar, placed 50 km apart.

### Results

Higher total pollen indexes were recorded in the Al Khor station (2931 pollen * day/$m^3$) compared to the Doha station (1618 pollen * day/$m^3$). Comparing the pollen spectrum between the sampling stations revealed that ten pollen types were found in common. Amaranthaceae and Poaceae airborne pollen constituted 73.5% and 70.9% of the total amount of pollen detected at the samplers of Al Khor station and Doha station. In both sampling sites, a very pronounced seasonality was shown; August–October appeared as the period with the most intense incidence of atmospheric herbaceous pollen, with 71% and 51% of the annual total counts in Al Khor and Doha stations, respectively. August (Al Khor, 21%; Doha, 9%), September (Al Khor, 33%; Doha, 26%), October (Al Khor, 17%; Doha, 16%) were the months in which the herbs pollen concentrations were highest.

[Intervention Review]

# Anti-IL-5 therapies for asthma

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## ABSTRACT

### Background

This is the second update of previously published reviews in the Cochrane Library (2015, first update 2017). Interleukin-5 (IL-5) is the main cytokine involved in the proliferation, maturation, activation and survival of eosinophils, which cause airway inflammation and are a classic feature of asthma. Studies of monoclonal antibodies targeting IL-5 or its receptor (IL-5R) suggest they reduce asthma exacerbations, improve health-related quality of life (HRQoL) and lung function in appropriately selected patients, justifying their inclusion in the latest guidelines.

### Objectives

To compare the effects of therapies targeting IL-5 signalling (anti-IL-5 or anti-IL-5Rα) with placebo on exacerbations, health-related quality-of-life (HRQoL) measures and lung function in adults and children with chronic asthma, and specifically in those with eosinophilic asthma refractory to existing treatments.

### Search methods

We searched CENTRAL, MEDLINE, Embase, and two trials registers, manufacturers' websites, and reference lists of included studies. The most recent search was 7 February 2022.

### Selection criteria

We included randomised controlled trials comparing mepolizumab, reslizumab and benralizumab versus placebo in adults and children with asthma.

### Data collection and analysis

Two review authors independently extracted data and analysed outcomes using a random-effects model. We used standard methods expected by Cochrane.

### Main results

Seventeen studies on about 7600 participants met the inclusion criteria. Six used mepolizumab, five used reslizumab, and six used benralizumab. One study using benralizumab was terminated early due to sponsor decision and contributed no data. The studies were predominantly on people with severe eosinophilic asthma, which was similarly but variably defined. One was in children aged 6 to 17 years; nine others included children over 12 years but did not report results by age group separately. We deemed the overall risk of bias to be low, with all studies contributing data of robust methodology. We considered the certainty of the evidence for all comparisons to be high overall using the GRADE scheme, except for intravenous (IV) mepolizumab and subcutaneous (SC) reslizumab because these are not currently licensed delivery routes.

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ORIGINAL ARTICLE

# Maternal vaccine hesitancy towards COVID-19 immunisation of children in Qatar: a population-based cross-sectional study

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**OBJECTIVES:** This study was conducted in Qatar to explore beliefs and attitudes among mothers towards coronavirus disease 2019 (COVID-19) vaccination for their children and to understand major factors influencing vaccine hesitancy among these mothers.

**METHODS:** A population-based, online cross-sectional survey was conducted between 15 October and 15 November 2020. A composite questionnaire incorporating a validated vaccine hesitancy tool was developed and administered in both English and Arabic. Approval was obtained from the local ethics committee. Participation was voluntary and offered to all adult residents of Qatar through an online link available on social media platforms and local news portals. Only adult respondents who self-identified as mothers were included in the present study. No personal identifying data were collected.

**RESULTS:** Of the mothers surveyed, 29.4% exhibited COVID-19 vaccine hesitancy regarding their children. This exceeded these mothers' rate of personal vaccine hesitancy (27.5%). Hesitancy rates varied significantly with ethnicity, with the highest among Qatari mothers (51.3%). Intention to vaccinate children did not differ significantly between mothers who accepted the vaccine for themselves and those who did not. Overall, the main reported concerns related to long-term vaccine safety. To a significant extent, mothers relied most on self-directed research on vaccine safety for decision-making.

**CONCLUSIONS:** The rate of maternal COVID-19 vaccine hesitancy exceeded both those mothers' rate of personal vaccine hesitancy and the hesitancy rate in the general population. The intention to vaccinate children was independent of maternal vaccination history. Factors influencing maternal vaccine hesitancy differ from those influencing personal hesitancy and require an informed public health response.

**KEY WORDS:** COVID-19, Vaccination hesitancy, Vaccination refusal, Qatar

## INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has brought the world to its knees, and vaccines are crucial in delivering us from this health catastrophe. Pandemics can be controlled through herd immunity, and the safest way to attain herd immunity is through vaccination [1].

To achieve herd immunity, a large proportion of the population must be immunised. The populations of many countries have high proportions of children under 18 years old, meaning that children must be vaccinated to achieve the immunisation levels required for herd immunity [2]. Moreover, highly exposed and vulnerable groups can be targeted via immunisation, making vaccines a more

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Article

# Toward deep observation: A systematic survey on artificial intelligence techniques to monitor fetus via ultrasound images

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## SUMMARY

**Several reviews have been conducted regarding artificial intelligence (AI) techniques to improve pregnancy outcomes. But they are not focusing on ultrasound images. This survey aims to explore how AI can assist with fetal growth monitoring via ultrasound image. We reported our findings using the guidelines for PRISMA. We conducted a comprehensive search of eight bibliographic databases. Out of 1269 studies 107 are included. We found that 2D ultrasound images were more popular (88) than 3D and 4D ultrasound images (19). Classification is the most used method (42), followed by segmentation (31), classification integrated with segmentation (16) and other miscellaneous methods such as object-detection, regression, and reinforcement learning (18). The most common areas that gained traction within the pregnancy domain were the fetus head (43), fetus body (31), fetus heart (13), fetus abdomen (10), and the fetus face (10). This survey will promote the development of improved AI models for fetal clinical applications.**

## INTRODUCTION

### Background

Artificial intelligence (AI) is a broad discipline that aims to replicate the inherent intelligence shown by people via artificial methods (Hassabis et al., 2017). Recently, AI techniques have been widely utilized in the medical sector (Miller and Brown, 2018). Historically, AI techniques were standalone systems with no direct link to medical imaging. With the development of new technology, the idea of 'joint decision-making' between people and AI offers the potential of boosting high performance in the area of medical imaging (Savadjiev et al., 2019).

In computer science, machine learning (ML), deep learning (DL), artificial neural network (ANN) and reinforcement learning (RL) are subset techniques of AI that are used to perform different tasks on medical images such as classification, segmentation, object identification, and regression (Fatima and Pasha, 2017; Kim et al., 2019b; Shahid et al., 2019). Diagnosis using computer-aided detection (CAD) has moved toward becoming AI automated process in the medical images (Castiglioni et al., 2021), which include most of the medical imaging data such as X-ray radiography, fluoroscopy, MRI, medical ultrasonography or ultrasound, endoscopy, elastography, tactile imaging, and thermography (Alzubaidi et al., 2021a, 2021b; Fujita, 2020). However, digitized medical images come with a plethora of new information, possibilities, and challenges. Therefore, AI techniques are able to address some of these challenges by showing impressive accuracy and sensitivity in identifying imaging abnormalities. These techniques promise to enhance tissue-based detection and characterization with the potential to improve diagnoses of diseases (Tang, 2020).

At present, the use of AI techniques in medical images has been discussed in depth across many medical disciplines, including identifying cardiovascular abnormalities, detecting fractures and other musculoskeletal injuries, aiding in diagnosing neurological diseases, reducing thoracic complications and conditions, screening for common cancers, and many other prognoses and diagnosis tasks (Castiglioni et al., 2021; Cheikh et al., 2020; Deo, 2015; Handelman et al., 2018; Miotto et al., 2017). Furthermore, AI techniques have shown the ability to provide promising findings when utilizing prenatal medical images, such as

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# Paediatric early warning systems: not a simple answer to a complex question

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## Abstract

Paediatric early warning systems (PEWS) to reduce in-hospital mortality have been a laudable endeavour. Evaluation of their impact has rarely examined the internal validity of the components of PEWS in achieving desired outcomes. We highlight the assumptions made regarding the mode of action of PEWS and, as PEWS become more commonplace, this paper asks whether we really understand their function, process and outcome.

**Keywords:** child health services; emergency service, hospital; health services research; mortality; paediatrics.

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ORIGINAL RESEARCH
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# Ultrasonographic Evaluation of the Hypospadiac Penis in Children

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**Introduction:** Identifying key anatomical features of the hypospadiac penis is crucial to better understanding this pathology and guiding surgical reconstruction plans, thereby achieving superior functional and cosmetic outcomes.

**Objective:** To Assess the feasibility and precision of penile ultrasonography (PUG) in determining key structural features for hypospadias cases (including distal extent of the spongiosal component of the urethral plate, to elucidate the healing process following tubularised incised-plate urethroplasty).

**Patients and Methods:** Twenty-five children with hypospadias were assessed using PUG prior to surgical repair and then again under general anesthesia. Preoperative images were acquired using ultrasonography in sagittal and transverse planes, then later compared with anatomical findings obtained during surgical repair of urethral hypoplasia.

**Results:** Median patient age was 1.2 years (range 0.5–12) and hypospadias types included coronal 17/25 (68%), mid-penile 5/25 (20%), and proximal penile 3/25 (12%). Distinct layers of the corpus spongiosa and mucosal layer, Buck fascia, tunica albuginea, glans, corpora cavernosa, and penile skin were delineated so that their spatial inter-relationship could be assessed. Distal extent of the spongiosal component of the urethral plate was determined by the mid-glans B-B line. The extent of urethral hypoplasia identified by PUG was relatively similar to measurements obtained intraoperatively.

**Conclusion:** PUG is a feasible and accurate approach to evaluating penile configuration in children with hypospadias. Distal extent of the spongiosal component of the urethral plate was accurately determined, hence PUG could potentially be used to improve surgical planning and appraisal of current repair procedures.

**Keywords: hypospadias, ultrasound, evaluation, urethral hypoplasia, penile anatomical disorders**

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## INTRODUCTION

Hypospadias is a common malformation of the penis in which abortive development of the ventral axis and corpus spongiosum leads to a range of short- and long-term effects (1–3). Delineating the anatomy of hypospadias is critical to better understanding this pathology. New techniques that can accurately detect and define structural features of hypospadias will help surgeons to

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ARTICLE

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# A diagnostic classifier for gene expression-based identification of early Lyme disease

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## Abstract

**Background** Lyme disease is a tick-borne illness that causes an estimated 476,000 infections annually in the United States. New diagnostic tests are urgently needed, as existing antibody-based assays lack sufficient sensitivity and specificity.

**Methods** Here we perform transcriptome profiling by RNA sequencing (RNA-Seq), targeted RNA-Seq, and/or machine learning-based classification of 263 peripheral blood mononuclear cell samples from 218 subjects, including 94 early Lyme disease patients, 48 uninfected control subjects, and 57 patients with other infections (influenza, bacteremia, or tuberculosis). Differentially expressed genes among the 25,278 in the reference database are selected based on ≥1.5-fold change, ≤0.05 *p* value, and ≤0.001 false-discovery rate cutoffs. After gene selection using a k-nearest neighbor algorithm, the comparative performance of ten different classifier models is evaluated using machine learning.

**Results** We identify a 31-gene Lyme disease classifier (LDC) panel that can discriminate between early Lyme patients and controls, with 23 genes (74.2%) that have previously been described in association with clinical investigations of Lyme disease patients or in vitro cell culture and rodent studies of *Borrelia burgdorferi* infection. Evaluation of the LDC using an independent test set of samples from 63 subjects yields an overall sensitivity of 90.0%, specificity of 100%, and accuracy of 95.2%. The LDC test is positive in 85.7% of seronegative patients and found to persist for ≥3 weeks in 9 of 12 (75%) patients.

**Conclusions** These results highlight the potential clinical utility of a gene expression classifier for diagnosis of early Lyme disease, including in patients negative by conventional serologic testing.

## Plain language summary

Lyme disease is a bacterial infection spread by ticks and there are nearly half a million cases a year in the United States. However, the disease is difficult to diagnose and existing laboratory tests have limited accuracy. Here, we develop a new genetic test, described as a Lyme disease classifier (LDC), for diagnosing early Lyme disease from blood samples by assessing the patient's response to the infection. We find that the LDC can identify early Lyme disease patients (those presenting with symptoms within weeks of a tick bite) accurately, even before standard laboratory tests turn positive. In the future, the LDC may be clinically useful as a test for Lyme disease to diagnose patients earlier in the course of their illness, thus guiding more timely and effective treatment for the infection.

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# Management of neuropathic bladder secondary to spina bifida: Twenty years' experience with a conservative approach

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**Introduction:** Treatment of neuropathic bladder secondary to spina bifida is an ongoing challenge. Although different management strategies and protocols are available in the literature, reliance on expert opinion remains fundamental. A conservative approach can be utilized, but patients must be closely monitored throughout the management process. The objective of this study was to review the management and outcomes of neuropathic bladder in spina bifida by appraising long-term bladder and renal function in patients treated at a medical center utilizing a conservative management style.

**Methods:** This is a single-center retrospective review of urology care for all spina bifida patients 5–19 years of age with a neuropathic bladder who attended follow-ups between April 2000 and April 2020. Only patients with more than 5 years of follow-up were included. Renal functions, continence and results of invasive video urodynamics (IUD) and any surgical interventions were recorded.

**Results:** Seventy-one patients (mean age = 10.5 years) were identified after exclusions. Bladder compliance between first and last IUDs increased significantly ($p = 0.0056$). Anticholinergic treatment was started at the first outpatient appointment. Intravesical botulinum toxin injection was the second line treatment in ten patients. 94% of patients had an end fill pressure below 40 cm $H_2O$ in their last IUD. 82% were socially continent (dry or occasional damp patches) with or without catheterisations at the age of 11.5 years. One patient in the cohort had bladder augmentation.

**Conclusion:** The optimal management of neuropathic bladder secondary to spina bifida remains controversial. Bladder and renal functional outcomes can be improved with close monitoring and less invasive management.

KEYWORDS

**spina bifida, neuropathic bladder, urodynamics, intermittent catheterisation, conservative, management**

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Review Article

# Functional recoverability post-pyeloplasty in children with ureteropelvic junction obstruction and poorly functioning kidneys: Systematic review

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**Keywords**
Hydronephrosis; Pyeloplasty; Recoverability; Renal function; Poorly functioning; Children

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## Summary

**Background**
The management of poorly functioning kidneys (PFK) associated with ureteropelvic junction obstruction (UPJO) is controversial. There is contradictory information about how to best manage these cases: pyeloplasty or nephrectomy?

**Objective**
To systematically summarize the available evidence concerning the effects of pyeloplasty on the differential renal function of PFK in children with unilateral UPJO, highlighting the ongoing challenges in their definition, management, and long-term follow-up. In addition, we aim to verify potential predictors of renal functional recoverability that could help clinicians choose candidates for pyeloplasty.

**Methods**
We searched several databases including PubMed, Embase, and Cochrane Library CENTRAL until August 20, 2021, according to the PRISMA guidelines. The following concepts were searched: pediatric, ureteropelvic junction obstruction, UPJO, pyeloplasty, recovery, split renal function, and differential renal function. We enrolled studies where the PFK was defined as preoperative differential renal function (DRF) $\leq$30% by renal scintigraphy. Potential predictors of renal functional recoverability were assessed and compared among studies. The quality of the included studies was evaluated using a modified version of the Newcastle—Ottawa scale (NOS).

**Results**
1499 citations perceived as relevant to screening were retrieved. After screening, 20 studies were included, comprising a total of 625 cases. The number of patients in each study varied between 5 and 84, while the average post-surgical follow-up duration ranged between 3 months and 180 months. The most significant preoperative predictive factor for postoperative functional recoverability was the baseline DRF, especially when antenatally diagnosed. The quality was considered average in a significant portion of included studies.

**Conclusion**
A significant proportion of PFK showed an increase of DRF post-pyeloplasty. However, no consistent predictive factors for functional recoverability have yet been determined apart from preoperative DRF. Until further evidence appears, pyeloplasty should be considered a valid option in the armamentarium of UPJO management in PFK.

## Introduction

Ureteropelvic junction obstruction (UPJO) is the most common form of upper urinary tract obstruction in children, with a reported incidence of 1:500 to 1:1250 live births [1]. Surgical intervention is indicated mainly when there is a progressive dilatation of the pelvis, deterioration of renal function, infection, significant obstructive drainage, and pain. Anderson-Hynes dismembered pyeloplasty is the gold-standard procedure, with success rates exceeding 90% regardless of access type (open, laparoscopic, or robot-assisted).

Pyeloplasty is indicated for patients whose kidneys have reasonable differential renal function (DRF), but the management of UPJO in patients with poorly functioning kidneys (PFK) is controversial. Some consider a cutoff of DRF

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# PCovNet: A presymptomatic COVID-19 detection framework using deep learning model using wearables data

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ABSTRACT

While the advanced diagnostic tools and healthcare management protocols have been struggling to contain the COVID-19 pandemic, the spread of the contagious viral pathogen before the symptom onset acted as the Achilles' heel. Although reverse transcription-polymerase chain reaction (RT-PCR) has been widely used for COVID-19 diagnosis, they are hardly administered before any visible symptom, which provokes rapid transmission. This study proposes PCovNet, a Long Short-term Memory Variational Autoencoder (LSTM-VAE)-based anomaly detection framework, to detect COVID-19 infection in the presymptomatic stage from the Resting Heart Rate (RHR) derived from the wearable devices, i.e., smartwatch or fitness tracker. The framework was trained and evaluated in two configurations on a publicly available wearable device dataset consisting of 25 COVID-positive individuals in the span of four months including their COVID-19 infection phase. The first configuration of the framework detected RHR abnormality with average Precision, Recall, and F-beta scores of 0.946, 0.234, and 0.918, respectively. However, the second configuration detected aberrant RHR in 100% of the subjects (25 out of 25) during the infectious period. Moreover, 80% of the subjects (20 out of 25) were detected during the presymptomatic stage. These findings prove the feasibility of using wearable devices with such a deep learning framework as a secondary diagnosis tool to circumvent the presymptomatic COVID-19 detection problem.

## 1. Introduction

The COVID-19 pandemic has been one of the most significant global events in this decade that have affected the whole world at the same time and marked the most crucial struggle of humanity against a highly contagious viral pathogen in modern times. The pathogen, namely Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), commonly known as the coronavirus, has caused approximately 491 million infection cases with about 6.1 million death tolls worldwide to date [1]. Despite the advancement of technology and healthcare protocols, the lack of preparedness for utilizing these technologies was a major lesson in this pandemic [2–4]. However, researchers from diverse sectors have come forward with their innovations and findings to fight back this pandemic by making effective use of our existing technologies, including the discovery of effective vaccines within the shortest timespan to date, improvement in the pandemic management employing digital technologies, widespread contact-tracing, fast and effective diagnosis methods, and new methods for detecting asymptomatic carriers.

SARS-CoV-2 has some similar characteristics (e.g., transmission

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# Challenges in the Management of Wilms Tumor in a Developing Country: A Twenty Years' Experience From a Single Center in Pakistan

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PMID: 35917164 DOI: 10.1097/MPH.0000000000002507

## Abstract

**Background:** Wilms Tumor (WT) is one of the most curable childhood cancers. High cure rates seen in the developed countries are not reproduced in developing countries. Lack of access to cancer treatment facilities, financial constraints, late presentation, and abandonment have previously been described. We reviewed our data over the last 20 years to highlight some of these challenges.

**Methods:** This is a retrospective chart review of children with WT at our center up to the age of 18 years between 1 November 1997 and 30 November 2017. Demographic details, presentation characteristics and treatment details were recorded. Factors associated with poor outcome were analyzed.

**Results:** Two hundred eleven children were registered; 117(55.5%) were males. Median age at presentation was 3 (range 0 to 18) years. Presentation data were available for 184/211 patients, staging details for 159/211 and metastatic status for 178/211. Of the available dataset, 60% presented without prior treatment, whereas 40% presented atleast after primary surgical excision. High-stage (stage III or above) disease was present in 79 (49.7%) patients; 61 (34.3%) was presented with metastases or recurrence; 63 (29.8%) abandoned or refused treatment; 99/172 (57.6%) patients finished treatment, 23 (13.4%) died during treatment, and 6 died before treatment. Of the 99 patients who finished treatment 83 (83.8%) are well off therapy; 15(15.2%) relapsed; 6 (40%) are alive after salvage therapy, while 9 (60%) died.

**Conclusions:** Our data highlights the challenges of managing WT in resource poor environments. Prior surgery, incomplete staging work-up and abandonment are some of the most frequently encountered barriers. A multipronged approach is required to overcome these challenges.

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GLOBAL ONCOLOGY: RESEARCH ARTICLE

# Evidence-based surgical guidelines for treating children with Wilms tumor in low-resource settings

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**Abbreviations:** GDG, Guideline Development Group; GRADE, grading for recommendations, assessment, development, and evaluation; GSG, Guideline Steering Group; LMIC, low- to middle-income country; WT, Wilms tumor.

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## Abstract

**Background:** Survival of Wilms tumor (WT) is > 90% in high-resource settings but < 30% in low-resource settings. Adapting a standardized surgical approach to WT is challenging in low-resource settings, but a local control strategy is crucial to improving outcomes.

**Objective:** Provide resource-sensitive recommendations for the surgical management of WT.

**Methods:** We performed a systematic review of PubMed and EMBASE through July 7, 2020, and used the GRADE approach to assess evidence and recommendations.

**Recommendations:** Initiation of treatment should be expedited, and surgery should be done in a high-volume setting. Cross-sectional imaging should be done to optimize preoperative planning. For patients with typical clinical features of WT, biopsy should not be done before chemotherapy, and neoadjuvant chemotherapy should precede surgical resection. Also, resection should include a large transperitoneal laparotomy, adequate lymph node sampling, and documentation of staging findings. For WT with tumor thrombus in the inferior vena cava, neoadjuvant chemotherapy should be given before *en bloc* resection of the tumor and thrombus and evaluation for viable tumor thrombus. For those with bilateral WT, neoadjuvant chemotherapy should be given for 6–12 weeks. Neither routine use of complex hilar control techniques during nephron-sparing surgery nor nephron-sparing resection for unilateral WT with a normal contralateral kidney is recommended. When indicated, postoperative radiotherapy should be administered within 14 days of surgery. Post-chemotherapy pulmonary oligometastasis should be resected when feasible, if local protocols allow omission of whole-lung irradiation in patients with nonanaplastic histology stage IV WT with pulmonary metastasis without evidence of extrapulmonary metastasis.

**Conclusion:** We provide evidence-based recommendations for the surgical management of WT, considering the benefits/risks associated with limited-resource settings.

**KEYWORDS**
guidelines, nephroblastoma, surgery, Wilms tumor

## 1 | INTRODUCTION

Wilms tumor (WT), one of the most common solid tumors, is highly curable with affordable interventions.[1] The majority (90%) of patients with WT in high-income countries survive with chemotherapy, adequate surgical local control, and radiation therapy when indicated. However, survival in low-resource settings remains poor (50% to < 30%), reflecting limitations in resources (physical and human) and a lack of process standardization.[2,3] The World Health Organization's Global Initiative for Childhood Cancer targets WT as one of six index cancers included in attempts to reduce disparities in childhood cancer outcomes.[4] Efforts to address resource limitations include workforce training and shared advocacy to establish sustainable resources required for multimodality therapy and family support. Although guidance from high-income countries is available, it may be difficult to implement in low- and middle-income countries (LMICs) due to differences in resources and health systems. For WT, a limited capacity to manage intraoperative bleeding and limited access to diagnostics and radiation therapy are key factors necessitating the adaptation of guidelines to address specific challenges in LMICs. The aim of this work is to provide resource-sensitive recommendations for the surgical management of pediatric WT in limited-resource settings.

## 2 | METHODS

### 2.1 | Clinical practice guidelines

The guidelines were developed following the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) method

# Avascular Necrosis and Time to Surgery for Unstable Slipped Capital Femoral Epiphysis: A Systematic Review and Meta-analysis

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Affiliations + expand

PMID: 35941089 DOI: 10.1097/BPO.0000000000002179

## Abstract

**Background:** Avascular necrosis (AVN) is a well-known complication of unstable slipped capital femoral epiphysis (SCFE) and its cause is multifactorial. Higher AVN rates have been reported with surgery undertaken between 24 hours to 7 days from the onset of symptoms. The current evidence regarding time to surgery and AVN rate remains unclear. The aim of our study was to investigate the rate of AVN and time to surgery in unstable SCFE.

**Methods:** A literature search of several databases was conducted. Eligibility criteria included all studies that reported AVN rates and time to surgery in unstable SCFE patients. We performed a meta-analysis using a random-effects model to pool the rate of AVN in unstable SCFE using different time to surgery subgroups (≤24 h, 24 h - 7 d and >7 d). Descriptive, quantitative and qualitative data were extracted.

**Results:** Twelve studies matched our eligibility criteria. In total, there were 434 unstable SCFE of which 244 underwent closed reduction (CR). The pooled AVN rates were 24% [95% CI: 16%-35%] and 29% [95% CI: 16%-45%] for the total and CR groups, respectively. The highest AVN rates were with surgery between 24 hours to 7 days, 42% and 54% for the total and CR groups, respectively. The lowest rates of AVN were with time to surgery ≤24 hours (22% and 21% respectively) and >7 days (18% and 29% respectively). These differences were not statistically significant. There was significant subgroup heterogeneity which was highest in the 24 hours - 7 days subgroup and lowest in the >7 days subgroup.

**Conclusions:** The cumulative evidence was not conclusive for an association between AVN rate and time to surgery. The overall AVN rates were lower in unstable SCFE patients who had surgery ≤24 hours and >7 days. However, treatment techniques were very variable and there was significant heterogeneity in the included studies. Multi-centre prospective studies are required with well-defined time to surgery outcomes.

**Level of evidence:** Level III/IV.

Archives of Gynecology and Obstetrics
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REVIEW

# The optimal route of progesterone administration for luteal phase support in a frozen embryo transfer: a systematic review

**Abdulla Almohammadi[1] · Ainharan Raveendran[2] · Mairead Black[3] · Abha Maheshwari[4]**

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## Abstract

**Objective** To investigate the optimal route of progesterone administration for luteal phase support in a frozen embryo transfer.
**Design** Systematic review.
**Patients** Women undergoing frozen embryo transfer (FET).
**Interventions** We conducted an extensive database search of Medline (PubMed), Embase, Web of Science, and Cochrane Trials Register using relevant keywords and their combinations to find randomized controlled trials (RCTs) comparing the routes (i.e., oral, vaginal, intramuscular) of progesterone administration for luteal phase support (LPS) in artificial FET.
**Main outcome measures** Clinical pregnancy, live birth, miscarriage.
**Results** Four RCTs with 3245 participants undergoing artificial endometrial preparation (EP) cycles during FET were found to be eligible. Four trials compared vaginal progesterone with intramuscular progesterone and two trials compared vaginal progesterone with oral progesterone. One study favored of vaginal versus oral progesterone for clinical pregnancy rates (RR 0.45, 95% CI 0.22–0.92) and other study favored intramuscular versus vaginal progesterone for clinical pregnancy rates (RR 1.46, 95% CI 1.21–1.76) and live birth rates (RR 1.62, 95% CI 1.28–2.05). Tabulation of overall evidence strength assessment showed low-quality evidence on the basis that for each outcome-comparison pair, there were deficiencies in either directness of outcome measurement or study quality.
**Conclusion** There was little consensus and evidence was heterogeneous on the optimal route of administration of progesterone for LPS during FET in artificial EP cycles. This warrants more trials, indirect comparisons, and network meta-analyses.
**PROPERO No** CRD42021251017.

**Keywords** Luteal phase support · Frozen embryo transfer · Progesterone · Live birth · Miscarriage

**What does this study add to the clinical work**

We sought to evaluate the current evidence regarding the optimal route of progesterone administration for luteal phase support in women undergoing FET cycles.

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## Introduction

Infertility is a prevalent public health issue, affecting 15% couples of reproductive age worldwide [1]. It is on the rise with 48 million couples and 186 million individuals infertile all over the world [2]. It is a life crisis with damaging psychosocial consequences in the form of marital instability, violence, divorce, social exclusion, stigmatization, and suicidal ideations [3]. Infertility is considered a personal

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Article

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# Protection of Omicron sub-lineage infection against reinfection with another Omicron sub-lineage

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Check for updates

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There is significant genetic distance between SARS-CoV-2 Omicron (B.1.1.529) variant BA.1 and BA.2 sub-lineages. This study investigates immune protection of infection with one sub-lineage against reinfection with the other sub-lineage in Qatar during a large BA.1 and BA.2 Omicron wave, from December 19, 2021 to March 21, 2022. Two national matched, retrospective cohort studies are conducted to estimate effectiveness of BA.1 infection against reinfection with BA.2 (N = 20,994; BA.1-against-BA.2 study), and effectiveness of BA.2 infection against reinfection with BA.1 (N = 110,315; BA.2-against-BA.1 study). Associations are estimated using Cox proportional-hazards regression models after multiple imputation to assign a sub-lineage status for cases with no sub-lineage status (using probabilities based on the test date). Effectiveness of BA.1 infection against reinfection with BA.2 is estimated at 94.2% (95% CI: 89.2–96.9%). Effectiveness of BA.2 infection against reinfection with BA.1 is estimated at 80.9% (95% CI: 73.1–86.4%). Infection with the BA.1 sub-lineage appears to induce strong, but not full immune protection against reinfection with the BA.2 sub-lineage, and vice versa, for at least several weeks after the initial infection.

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CASE REPORT

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# Severe pulmonary hemorrhage in a 3-week-old neonate with COVID-19 infection: A case report

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**Abstract**

Our patient is a 3-week-old female neonate, presented with complaints of low-grade fever and a congested nose for one day. Eventually, she developed progressive desaturation, hypotension, and poor perfusion due to severe pulmonary hemorrhage. Then, she developed cardiac arrest and was declared dead.

**KEYWORDS**

COVID-19, newborn, pulmonary hemorrhage, SARS-CoV-2, sepsis

## 1 | INTRODUCTION

During the SARS-CoV-2 pandemic, the majority of pediatric cases presented with lung involvement as the main disease, with the severity of symptoms ranging from mild pneumonia to severe lung injury and ARDS. Emerging studies found that some patients may experience uncommon complications, such as thrombotic or hemorrhagic episodes.[1] The cases of pulmonary hemorrhage have been reported in adults with COVID-19 infection; however, reports about similar presentations in pediatrics are rare. We present a case of a 3-week-old neonate with COVID-19 infection and no other underlying comorbidities but a fatal pulmonary hemorrhage. Our case report demonstrates the unusual presentation of COVID-19 infection in neonates and presents the challenges associated with it.

## 2 | CASE PRESENTATION

The patient is a 3-week-old female infant, a product of full-term pregnancy and uneventful normal vaginal delivery. She was delivered to a 37-year-old healthy GBS-negative mother. Her birth weight was appropriate for her

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RESEARCH PAPER

# Health research-strengthening and capacity development: Research support system model in an academic healthcare system

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## ABSTRACT

Introduction: Healthcare research contributes to the well-being of a population; hence, it is important to use the right system to ensure that junior researchers develop the required skills. Current research-strengthening and capacity development programs might lack a research process-based common framework or model leading to variable and suboptimal outcomes. This study aimed to describe the development and evaluation of a model for health research-capacity development at both individual and institutional levels in a Joint Commission International-accredited governmental healthcare organization in Qatar.

Methods: This retrospective observational study evaluated a research support system employed in Qatar for 1 year and constituted of16 stations, each covering a different topic and supported by an experienced faculty member. We recorded how many faculty members were involved and how many people accessed which stations. We developed an outcomes logistic model and obtained feedback about their experience of using the research support system through a short survey.

Results: Twenty-one faculty members supported a total of 77 participants, representing various professions and specialties. The majority of the participants received support on multiple stations, and the most solicited were study design and methodology (n = 45, 58.4%) and research idea (n = 29, 37.7%). The most common type of research that participants required support for was clinical research (n = 65, 84.4%). Moreover, 58.4% of the participants answered the survey, and their responses attested to their perceived benefit of making use of the research support system.

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RESEARCH Open Access

# Optimising care and follow-up of adults with achondroplasia

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## Abstract

**Background:** Achondroplasia is a genetic condition that can cause complications across the lifespan. While complications in childhood are well documented, the natural history of achondroplasia in adults has, until recently, been relatively lacking, and little is known about the care they receive or how they access it. The European Achondroplasia Forum undertook two exploratory surveys, one for healthcare professionals (HCPs) and one for patient advocacy group (PAG) representatives, to gain an understanding of current practices of the transition process of individuals with achondroplasia from paediatric to adult services and how adults perceive their care.

**Results:** Most HCP respondents followed up more children than adults, and 8/15 responded that individuals did not transition to an adult multidisciplinary team (MDT) after paediatric care. Of 10 PAG respondents, none considered the experience of transition to adult services as good or very good and 50% considered it to be poor or very poor. A total of 64% (7/11) described the coordination of transition to adult services as "Not satisfactory" or "Poor". HCPs and PAG representatives largely agreed on the core specialists involved in adult care (orthopaedic surgeons, physiotherapists, rehabilitation specialists, rheumatologists, clinical geneticists). However, there was a discrepancy in the understanding of healthcare needs outside of this, with PAG representatives selecting neurosurgeons and genetic counsellors, while HCPs selected pulmonologists and obstetricians/gynaecologists. There was agreement between HCP and PAG respondents on the key barriers to effective care of adults with achondroplasia, with lack of an adult MDT, lack of interest from individuals in accessing care, and less experience in adult than paediatric MDTs ranking highly.

**Conclusions:** This study indicates that the care and follow up of adults with achondroplasia is challenging. Individuals are often lost to, or decline, follow up as they leave paediatric care, and it is largely unknown how, where, and why adults with achondroplasia access care later in life. Lifelong, multidisciplinary specialist care led by an identified physician should be accessible to all individuals with achondroplasia. It is important to ensure barriers to optimal care are addressed to enable access to appropriate care for all individuals with achondroplasia.

**Keywords:** Achondroplasia, European Achondroplasia Forum, Adult, Transition, Guiding principles, Management, Recommendations

## Background

Achondroplasia is an autosomal dominant genetic condition that can cause complications across the lifespan, thereby requiring lifelong management [1–5]. It is caused by a recurrent pathogenic variant in the fibroblast growth factor receptor 3 (*FGFR3*) gene [6, 7]. Many complications such as foramen magnum stenosis,

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ORIGINAL ARTICLE

# Staff perceptions and challenges of the single-family room design—Experience of a greenfield level4 neonatal intensive care unit in the Middle East

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## Abstract

**Aim:** This study was undertaken to specifically identify challenges associated with the popular single-family room (SFR) design in our new neonatal intensive care unit (NICU), so as to reap the full benefits of this architectural model.

**Methods:** A survey was sent to all 223, newly recruited staff on our NICU. Questions explored staff perceptions of family experience, safety and staff's experience of the SFR in comparison with the open bay model.

**Results:** We obtained a response rate of 66%. Most staff perceived SFR as having a positive impact on communication with families, privacy, feasibility for skin-to-skin contact, reduction in noise levels and family access to their baby. There were however concerns raised about patient safety and isolation of staff and families in the SFR architecture. Lack of opportunities to leave the patient room for breaks and increased physical demands were highlighted. Staff also felt physically and emotionally less well supported.

**Conclusion:** Whilst the SFR configuration was felt to be beneficial for infants and families, staff shared their perceived concerns regarding infant safety and isolation and staff satisfaction, and implied modifications to workflows. The survey findings resulted in re-organisation of our staff numbers and communication systems and further facilitation of parent interactions in order to optimise benefits of SFR design.

KEYWORDS
infant and family-centred developmental care, newborn infant, NICU design, single-family room

**Abbreviations:** SFR, single-family room; NICU, neonatal intensive care unit; IFCDC, infant- and family-centred developmental care; FINE, family and infant neurodevelopmental education.

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# Long term outcome of babies with pulmonary hypertension

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ABSTRACT

Neonatal pulmonary hypertension (PH) is associated with many severe congenital abnormalities (congenital diaphragmatic hernia) or acquired cardiorespiratory diseases such as pneumonia, meconium aspiration and bronchopulmonary dysplasia (BPD). If no cause is found it may be labelled idiopathic persistent pulmonary hypertension of the newborn. Although PH may result in life threatening hypoxia and circulatory failure, in the majority of cases, it resolves in the neonatal period following treatment of the underlying cause. However, in some cases, neonatal PH progresses into infancy and childhood where symptoms include failure to thrive and eventually right heart failure or death if left untreated. This chronic condition is termed pulmonary vascular hypertensive disease (PHVD). Although classification and diagnostic criteria have only recently been proposed for pediatric PHVD, little is known about the pathophysiology of chronic neonatal PH, or why pulmonary vascular resistance may remain elevated well beyond infancy. This review explores the many factors involved in chronic PH and what implications this may have on long term outcome when the disease progresses beyond the neonatal period.

## 1. Introduction

Neonatal pulmonary hypertension (PH) is associated with a broad range of potentially serious neonatal cardiorespiratory diseases with high morbidity and mortality [1]. Some manifest within hours of birth with acute hypoxemic respiratory failure such as persistent pulmonary hypertension of the newborn (PPHN) or meconium aspiration pneumonia, and others may evolve over hours or days following a brief "honeymoon" period as seen congenital diaphragmatic hernia (CDH) [2]. In conditions like bronchopulmonary dysplasia (BPD), where prematurity plays an important role, there may be considerable variation in presentation depending upon the degree of lung injury and other inflammatory triggers [3,4]. In the clinical setting of PH, the course is closely related to the ability of the right ventricle to cope and the left ventricle to maintain an adequate systemic cardiac output. In acute PH, a vicious spiral may occur, where poor gas exchange leads to worsening hypoxemia, hypotension, acidosis and impairment of cardiac function. In extreme cases, the use of extracorporeal membrane oxygenation support (ECMO) may be life-saving to allow enough time for primary disease resolution or for pulmonary vascular resistance to normalize following pulmonary vasodilator therapy [5]. Occasionally, outcome may not be favorable with the development of chronic PH and progressive right heart failure.

While there is a large body of literature describing the acute situation of these respiratory conditions, there is a marked paucity of information on what happens beyond this critical acute phase with specific relevance to survivors of neonatal PH. Questions remain as to how pulmonary hypertension may develop in some conditions and progress into infancy and childhood, what trigger factors may promote this maladaptive response, and ultimately how chronic PH (cPH) influences long term outcome and quality of life [6–8]. This may result partly from changes in speciality as neonatal patients graduate toward pediatrics or pediatric intensive care. For example, a neonate with chronic lung disease and PH may require long-term ventilation via a tracheostomy, and there is probably a wide variation around the world at which point pediatric teams take over the care and management of these complex patients [9]. This may have significant influence on follow-up, especially where PH is followed by specialist pediatric pulmonary hypertension clinics, which may only be available in tertiary centres.

There is paucity of data to describe the long term outcome of babies

*Abbreviations:* PH, Pulmonary Hypertension; PHVD, Pulmonary hypertensive vascular disease; PVR, Pulmonary vascular resistance; CDH, Congenital diaphragmatic hernia; CHD, Congenital heart disease.

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# Transcatheter interventions in patients with a Fontan circulation: Current practice and future developments

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The Fontan operation represents the last of multiple steps that are offered a wide range of congenital cardiac lesions with a single ventricle (SV) physiology. Nowadays this surgical program consists of a total cavopulmonary connection (TCPC), by anastomosing systemic veins to the pulmonary arteries (PAs), excluding the right-sided circulation from the heart. As a result of imaging, surgical, percutaneous, and critical care improvements, survival in this population has steadily increased. However, the Fontan physiology chronically increases systemic venous pressure causing systemic venous congestion and decreased cardiac output, exposing patients to the failure of the Fontan circulation (FC), which is associated with a wide variety of clinical complications such as liver disease, cyanosis, thromboembolism, protein-losing enteropathy (PLE), plastic bronchitis (PB), and renal dysfunction, ultimately resulting in an increased risk of exercise intolerance, arrhythmias, and premature death. The pathophysiology of the failing Fontan is complex and multifactorial; i.e., caused by the single ventricle dysfunction (diastolic/systolic failure, arrhythmias, AV valve regurgitation, etc.) or caused by the specific circulation (conduits, pulmonary vessels, etc.). The treatment is still challenging and may include multiple options and tools. Among the possible options, today, interventional catheterization is a reliable option, through which different procedures can target various failing elements of the FC. In this review, we aim to provide an overview of indications, techniques, and results of transcatheter options to treat cavopulmonary stenosis, collaterals, impaired lymphatic drainage, and the management of

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# Automated quantification of penile curvature using artificial intelligence

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**Objective:** To develop and validate an artificial intelligence (AI)-based algorithm for capturing automated measurements of Penile curvature (PC) based on 2-dimensional images.

**Materials and methods:** Nine 3D-printed penile models with differing curvature angles (ranging from 18 to 88°) were used to compile a 900-image dataset featuring multiple camera positions, inclination angles, and background/lighting conditions. The proposed framework of PC angle estimation consisted of three stages: automatic penile area localization, shaft segmentation, and curvature angle estimation. The penile model images were captured using a smartphone camera and used to train and test a Yolov5 model that automatically cropped the penile area from each image. Next, an Unet-based segmentation model was trained, validated, and tested to segment the penile shaft, before a custom Hough-Transform-based angle estimation technique was used to evaluate degree of PC.

**Results:** The proposed framework displayed robust performance in cropping the penile area [mean average precision (mAP) 99.4%] and segmenting the shaft [Dice Similarity Coefficient (DSC) 98.4%]. Curvature angle estimation technique generally demonstrated excellent performance, with a mean absolute error (MAE) of just 8.5 when compared with ground truth curvature angles.

**Conclusions:** Considering current intra- and inter-surgeon variability of PC assessments, the framework reported here could significantly improve precision of PC measurements by surgeons and hypospadiology researchers.

KEYWORDS

**penile curvature, artificial intelligence, machine learning, hypospadias, chordee**

## Introduction

Penile curvature (PC) denotes an abnormal bending of the penile shaft that can occur in either congenital or acquired pathologies of the male external genitalia. The most common underlying congenital pathology is hypospadias which occurs in ∼1:250 male live births, with roughly one quarter to one third of cases also displaying substantial PC (Baskin et al., 1996; Stojanovic et al., 2011; Abbas and McCarthy, 2016). Hypospadias-associated

# Impact of Surgical Rejuvenation on Visual Processing and Character Attribution of Periorbital Aging

Thanapoom Boonipat [1], Amjed Abu-Ghname [1], Jason Lin [1], Esperanza Garcia-Gonzalo [1], Uldis Bite [1], Mitchell A Stotland [1]

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## Abstract

**Background:** The perceptual response to aging changes in the periorbital region and the effects of surgical rejuvenation on that response have not been elucidated. The authors examined the reflexive visual response to periorbital aging before and after brow lift and upper blepharoplasty surgery and investigated how observers' character attributions of the images were affected by the rejuvenative intervention.

**Methods:** Preoperative and postoperative photographs were obtained of patients with brow ptosis and dermatochalasis who underwent brow lift and blepharoplasty. Forty observers examined each image while an infrared eye-tracking camera continuously recorded their eye movements. The observers rated the images with respect to character attributes (attractiveness, trustworthiness, sociability, healthiness, and capability) on a scale of one to seven.

**Results:** Fourteen patients who underwent brow lift and blepharoplasty were identified and studied. The surgical intervention was found to increase observers' attention to the eye and brow region, while decreasing relative attention to the forehead and lower eyelid areas; increase the two-dimensional surface area of the forehead and eye and brow zones in a manner directly associated with the measured changes in visual attention; and significantly increase the ratings for all five positively valanced character attributes compared with preoperative controls.

**Conclusions:** The authors provide an important combination of explicit and implicit data illustrating how surgical rejuvenation unveils the periorbital region to the observer. This change in pattern of inspection was associated with an improvement in the perception of character.

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ORIGINAL ARTICLE

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# Three centers experience with device closure of congenital Gerbode-type perimembranous ventricular septal defects

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## Abstract

**Objectives:** We aim to evaluate our experience with interventional closure of Gerbode-type perimembranous ventricular septal defects (pmVSDs).

**Methods:** We performed three-center retrospective data review of patients with congenital indirect Gerbode-type pmVSDs treated percutaneously between August 2017 and May 2021. Standard safety and latest follow-up outcomes were assessed.

**Results:** Ten patients (six females) were identified with a median age of 6.8 years (range: 2.5–54) and a median weight of 26.5 kg (range: 12–88). The median left ventricular defect size was 10 mm (range: 3–15.5). On baseline ultrasound, 6 patients had absent subaortic rim , 6 patients had trivial aortic regurgitation, and 3 patients had tear-drop-type (small) aortic cusp prolapse. The tricuspid regurgitation was graded II ($n = 5$) and III ($n = 5$). Five Lifetech Konar-Multifunctional occluders, four Amplatzer duct occluders II and one Amplatzer duct occluder I were implanted. The median fluoroscopy time was 10.4 min (range: 4.3–20.2). Pre-existing aortic regurgitations remained identical. One new aortic regurgitation was identified before discharge and remained trivial after 48 months of follow-up. No heart block or tricuspid stenosis was observed on a median follow-up of 17 months (range: 3–48). All patients are symptom-free with complete shunt closure and significant regression or resolution of tricuspid regurgitation.

**Conclusions:** Despite anatomical challenges, interventional closure of congenital indirect Gerbode-type pmVSD appears to be feasible, safe, and most importantly clinically effective using different commercially available devices. Amplatzer duct occluder II and Lifetech Konar-Multifunctional occluder offer interesting specifications to retrogradely target this specific defect with success.

KEYWORDS

device closure, Gerbode defect, perimembranous ventricular septal defect

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# Isolation and characterization of *Vibrio owensii* from Palk Bay and its infection study against post larvae of *Litopenaeus vannamei*

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ABSTRACT

Vibrio is heterotrophic ubiquitous marine bacteria that plays dual role as putative halobiont and potential pathogen. Environment and diseases are inextricable hence the role of vibrio as a potential pathogen in the natural environment must be comprehended. Hence the present study aims at investigating the pathogenicity of *Vibrio owensii* on the post larvae of *Litopenaeus vannamei*. *V. owensii* isolated from the marine natural habitat of the Palk Bay province in India was highly resistant to ampicillin, methicillin, tetracycline and vancomycin. The strain also lacked pathogenicity against the post larvae of *L. vannamei* due to the absence of major virulence factors *viz.* Chitinase, phospholipase and hemolytic activity. Presumably this is the first report on the occurrence of *V. owensii* in the Indian waters therefore there arises a need to carry out more serious research on the pathogenicity of this species on other commercial crustaceans reared in the Indian aquaculture settings in order to apprehend its role as potential pathogen or the contrary.

## 1. Introduction

Vibrio species are heterotrophic indigenous marine bacterium that plays a major role in the marine ecosystem [1]. However, some species of Vibrio poses a serious threat to the marine environment as potential pathogens and accounts for substantial economic loss globally due to disease outbreak in aquaculture farms and the natural marine habitat [2–4]. *Vibrio harveyi, V. campbellii* and *V. owensii* belonging to the clade Harveyi are recognized as most predominant pathogenic species causing life threatening Vibriosis in crustaceans, molluscs, corals and finfish [3–5]. So far, twelve *Vibrio* species have been identified within the Harveyi clade [6,7] and most evince extremely close evolutionary relationship and similar biological characteristics which make it highly difficult to differentiate them based on 16S rRNA gene sequencing [8,9]. Hence, a multifaceted approach has been suggested for effective identification and differentiation of the members of this clade [9,10] which involves the analysis of housekeeping genes *viz.* gyrB, topA, mreB, pyrH, rpoA or recA along with phenotypic analysis [7,8,10].

All the members of this clade possess virulence factors however the rationale behind their pathogenicity remains elusive [11]. Intriguingly, extracellular proteins of *V. harveyi* have significant sequence similarity with that of the virulence associated proteins of human pathogens, such as *Salmonella, Shigella* and *Bacillus* species [12]. Earlier studies indicated that extracellular products (ECPs) function as important virulence determinants for several *V. harveyi* strains and several extracellular enzymes and lipases were associated with tissue damage associated pathogenicity [4,13,14]. Moreover, a cell wall component lipopolysaccharide (LPS) of *V. harveyi* strains, also exhibits pathogenicity [15]. Findings across the globe inferred that the infectivity of *V. harveyi* strains can also be ascribed to the other virulence factors, such as a phage-encoded factor [16–18], and production of exotoxins [17]. This is substantiated by the fact that the virulence of naïve *V. harveyi* and

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# BCG Vaccine-associated Complications in a Large Cohort of Children With Combined Immunodeficiencies Affecting Cellular and Humoral Immunity

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## Abstract

**Aims:** To present the details of Bacillus Calmette-Guérin (BCG)-vaccine associated complications (VACs) in combined immunodeficiencies (CID) patients.

**Methods:** Five centers participated in this retrospective study and completed a data form, which included general patients' information, clinical and laboratory data.

**Results:** Among 236 CID patients, 127 were BCG vaccinated. 41.9% of patients with family history of CID and 17.1% who were diagnosed by screening were BCG vaccinated. Twenty-three patients (18.1%) developed BCG-VACs. The median age of VACs was 6 months and the median time from vaccination to complications was 6 months. The highest rate of BCG-VACs was recorded in patients receiving the Russian BCG strain compared to the Tokyo and Danish strains. Univariate analysis of T-lymphocyte subsets showed increased odds of BCG complications in patients with CD3+, CD4+, and CD8+ counts of ≤250 cells/μL. Only CD8 + count ≤250 cells/μL had increased such odds on multivariate analysis. VACs were disseminated in 13 and localized in 10 patients. Localized complication occurred earlier after vaccination (median: 4 months) compared with disseminated ones (median: 7 months). There were no significant associations between sex, administered vaccine strain, serum immunoglobulins levels, lymphocyte subsets counts, and the chance of having either localized or disseminated BCG-related complications.

**Coclusions:** Although contraindicated, many patients with CID continue to be vaccinated with BCG. Low CD8 + count is a risk factor for BCG-related complications and localized complications occurred earlier than disseminated ones. Considerations should be undertaken by health care authorities especially in countries with high incidence of CID to implement newborn screening, delay the time of BCG vaccine administration beyond 6 months of age and to use the relatively safer strains like the Danish and Tokyo ones.

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# Viral metagenomics analysis of stool specimens from children with unresolved gastroenteritis in Qatar

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ABSTRACT

Acute gastroenteritis (AGE) is associated with significant global morbidity and mortality, especially among children under five years of age. Viruses are well established as etiologic agents of gastroenteritis since they are the most common pathogens that contribute to the disease burden in developing countries. Despite the advances in molecular diagnosis, a substantial proportion of AGE etiology remain unresolved. We implemented a viral metagenomics pipeline to determine the potential viral etiology associated with AGE among children under the age of five years in Qatar with undiagnosed etiology. Following enriching for the viral genome, ~1.3 billion sequences were generated from 89 stool specimens using the Illumina HiSeq platform, of which 7% were mapped to viral genomes. Human viruses were detected in 34 specimens (38.2%); 14 were adenovirus, nine coxsackievirus A16, five rotavirus (G9P[8] and G4P[8]), four norovirus (GII), one influenza A virus (H3), and one respiratory syncytial virus A (RSVA). In conclusion, the viral metagenomics approach is useful for determining AGE's etiology when routine molecular diagnostic assays fail.

## 1. Introduction

Acute gastroenteritis constitutes a significant health burden worldwide, especially in children residing in developing countries (Lakhan et al., 2013). (Chow et al., 2010). Diarrhea ranks as the fourth cause of mortality among children after pre-term birth complications, lower respiratory infections, and intrapartum diseases (Perin et al., 2022). Viruses including rotavirus, norovirus, astrovirus, and adenovirus are considered the major cause of diarrhea in children. (Clark and McKendrick, 2004; do Socorro Fôro Ramos et al., 2021; Fields et al., 2007; Middleton, 1996; Oude Munnink and van der Hoek, 2016). Worldwide, rotavirus infections remain a major cause of diarrhea mortality in children younger than five years (Troeger et al., 2018). While already lifesaving in developed countries, rotavirus vaccines are less effective in developing countries (Tissera et al., 2017) due to higher early in life transmission rates of rotavirus infection (Steele et al., 2016) and inadequate vaccination coverage or accessibility (Rheingans et al., 2012). Additionally, bacteria such as *Campylobacter* spp. and *Clostridium difficile* as well as parasites such as *Giardia lamblia* and *Cryptosporidium* spp. are important causes of AGE (Meyer et al., 2020).

The Global Burden of Diseases (GBD) study assessed the deaths and etiologies of diarrhea in 195 countries between 1990 and 2016. The authors reported that the incidence of rotavirus infection was the highest in children younger than five years with diarrhea, followed by *campylobacter* spp., enterotoxigenic *E. coli* and shigella (Troeger et al., 2018). Similarly, the Global Enteric Multicenter Study (GEMS) reported that the majority of moderate-to-severe diarrhea among children under five years of age in sub-Saharan Africa and South Asia was attributable

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# Prognostic Model of ICU Admission Risk in Patients with COVID-19 Infection Using Machine Learning

**Khandaker Reajul Islam [1], Jaya Kumar [1,*], Toh Leong Tan [2], Mamun Bin Ibne Reaz [3], Tawsifur Rahman [4], Amith Khandakar [4], Tariq Abbas [5], Md. Sakib Abrar Hossain [4], Susu M. Zughaier [6] and Muhammad E. H. Chowdhury [4,*]**

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**Abstract:** With the onset of the COVID-19 pandemic, the number of critically sick patients in intensive care units (ICUs) has increased worldwide, putting a burden on ICUs. Early prediction of ICU requirement is crucial for efficient resource management and distribution. Early-prediction scoring systems for critically ill patients using mathematical models are available, but are not generalized for COVID-19 and Non-COVID patients. This study aims to develop a generalized and reliable prognostic model for ICU admission for both COVID-19 and non-COVID-19 patients using best feature combination from the patient data at admission. A retrospective cohort study was conducted on a dataset collected from the pulmonology department of Moscow City State Hospital between 20 April 2020 and 5 June 2020. The dataset contains ten clinical features for 231 patients, of whom 100 patients were transferred to ICU and 131 were stable (non-ICU) patients. There were 156 COVID positive patients and 75 non-COVID patients. Different feature selection techniques were investigated, and a stacking machine learning model was proposed and compared with eight different classification algorithms to detect risk of need for ICU admission for both COVID-19 and non-COVID patients combined and COVID patients alone. C-reactive protein (CRP), chest computed tomography (CT), lung tissue affected (%), age, admission to hospital, and fibrinogen parameters at hospital admission were found to be important features for ICU-requirement risk prediction. The best performance was produced by the stacking approach, with weighted precision, sensitivity, F1-score, specificity, and overall accuracy of 84.45%, 84.48%, 83.64%, 84.47%, and 84.48%, respectively, for both types of patients, and 85.34%, 85.35%, 85.11%, 85.34%, and 85.35%, respectively, for COVID-19 patients only. The proposed work can help doctors to improve management through early prediction of the risk of need for ICU admission of patients during the COVID-19 pandemic, as the model can be used for both types of patients.

**Keywords:** intensive care unit; COVID-19; early prediction; machine learning; clinical biomarkers

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## 1. Introduction

The COVID-19 pandemic began in Wuhan, China at the end of 2019, and spread quickly throughout the world [1]. Some countries experienced more than one wave of the pandemic. As of 11 July 2022, globally there have been around 560 M confirmed cases and around 6.3 M deaths caused by COVID-19 [2]. This novel coronavirus mostly affects a

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# Ensemble Transfer Learning for Fetal Head Analysis: From Segmentation to Gestational Age and Weight Prediction

**Mahmood Alzubaidi [1,*,†], Marco Agus [1,†], Uzair Shah [1], Michel Makhlouf [2], Khalid Alyafei [2] and Mowafa Househ [1,*]**

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**Abstract:** Ultrasound is one of the most commonly used imaging methodologies in obstetrics to monitor the growth of a fetus during the gestation period. Specifically, ultrasound images are routinely utilized to gather fetal information, including body measurements, anatomy structure, fetal movements, and pregnancy complications. Recent developments in artificial intelligence and computer vision provide new methods for the automated analysis of medical images in many domains, including ultrasound images. We present a full end-to-end framework for segmenting, measuring, and estimating fetal gestational age and weight based on two-dimensional ultrasound images of the fetal head. Our segmentation framework is based on the following components: (i) eight segmentation architectures (UNet, UNet Plus, Attention UNet, UNet 3+, TransUNet, FPN, LinkNet, and Deeplabv3) were fine-tuned using lightweight network EffientNetB0, and (ii) a weighted voting method for building an optimized ensemble transfer learning model (ETLM). On top of that, ETLM was used to segment the fetal head and to perform analytic and accurate measurements of circumference and seven other values of the fetal head, which we incorporated into a multiple regression model for predicting the week of gestational age and the estimated fetal weight (EFW). We finally validated the regression model by comparing our result with expert physician and longitudinal references. We evaluated the performance of our framework on the public domain dataset HC18: we obtained 98.53% mean intersection over union (mIoU) as the segmentation accuracy, overcoming the state-of-the-art methods; as measurement accuracy, we obtained a 1.87 mm mean absolute difference (MAD). Finally we obtained a 0.03% mean square error (MSE) in predicting the week of gestational age and 0.05% MSE in predicting EFW.

**Keywords:** image segmentation; ensemble transfer learning; fetal head; gestational age; estimated fetal weight; ultrasound



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## 1. Introduction

Ultrasonic imaging, also known as ultrasound, is frequently utilized in clinical assessment since it does not include ionizing radiation, and it is less expensive than computed tomography (CT) and magnetic resonance imaging (MRI) [1]. Women usually have one to three ultrasounds during pregnancy. If the lady is pregnant with twins or is at high risk, ultrasounds may be required more frequently [2]. Ultrasound may be utilized in various prenatal diagnostic situations, including: confirming the pregnancy and the position of the fetus, calculating the gestational age of the fetal baby, verifying the number of fetal bodies, examining fetal development, examining the amounts of the placenta and amniotic fluid, identifying congenital disabilities, looking into complications, and other prenatal tests [3]. When ultrasound is routinely used in early pregnancy, it will result in an earlier detection of problems and an improved management of pregnancy complications, which is better than relying on clinical indicators such as bleeding in early pregnancy [4]. Halle et al. [5]

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RESEARCH

# The Utility of Serial Echocardiography Parameters in Management of Newborns with Congenital Diaphragmatic Hernia (CDH) and Predictors of Mortality

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## Abstract

Ventricular dysfunction may be found in 40% of newborns with CDH, and is not only a predictor of disease severity, but also mortality and need for ECMO. We conducted this study to assess the utility of serial echocardiography in management of newborns with CDH and their survival outcomes. This is a retrospective study, wherein the demographic, clinical and echocardiographic data from our local CDH registry and hospital clinical database were analyzed to study the correlation of timed echocardiographic findings with mortality and other outcomes. Fourty-two newborns with CDH were admitted during the study period (M/F:19/23), with median gestation of 38 weeks (IQR:36–39) and birth weight of 2.83 kg (IQR 2.45–3.17). Thirty-one were left-sided, seven right, one central, and three bilateral hernias. Twelve infants (28%) died in early infancy. Three infants were excluded from analysis due to either palliation at birth or significant cardiac anomaly. A total of 137 echos from 39 infants were analyzed. Seventy percent of newborns who died and had an echo within the first 72 h, were noted to have suffered from moderate to severe PH. Birth weight < 2.8 kg, RVSP > 45.5 in the first 72 h and postoperative VIS > 23.5 and RSS > 4.3 were good predictors of mortality. Markers of elevated pulmonary pressures and cardiac function were useful in guiding therapy. Serial timed functional echocardiography (f-Echo) monitoring allows targeted therapy of patients with CDH. Birth weight, initial severity of pulmonary hypertension and postoperative RSS and VIS may be useful in predicting mortality.

**Keywords** Congenital diaphragmatic hernia · Pulmonary hypertension · Functional echocardiography · Cardiac dysfunction · Mortality

## Abbreviations

| | |
|---|---|
| MAP | Mean Airway pressure |
| RVSP | Right Ventricular Systolic Pressure |
| PAAT | Peak Acceleration Time |
| RVET | Right ventricular ejection time |
| TAPSE | Tricuspid annular plane systolic excursion |
| VIS | Vasoactive Inotropic score |
| RSS | Respiratory severity score |
| f-Echo | Functional echocardiography |
| PH | Pulmonary hypertension |
| PPHN | Persistent pulmonary hypertension of newborn |
| PDA | Patent Ductus Arteriosus |
| ASD | Atrial septal defect |
| VSD | Ventricular septal defect |
| ECMO | Extracorporeal Membrane Oxygenation |

## Background

Congenital diaphragmatic hernia (CDH) is a life-threatening defect in the developing diaphragm's integrity [1], with a reported incidence of less than 3 per 10,000 live births [2], and is often accompanied by other congenital anomalies. Management of newborn infants with CDH requires a high skill set, with multidisciplinary team involvement, starting from the point of antenatal diagnosis. Despite improved outcomes over the years [3],

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# Effects of SARS-CoV-2 Alpha, Beta, and Delta variants, age, vaccination, and prior infection on infectiousness of SARS-CoV-2 infections

Suelen H. Qassim[1,2,3†], Mohammad R. Hasan[4†], Patrick Tang[4†], Hiam Chemaitelly[1,2,3], Houssein H. Ayoub[5], Hadi M. Yassine[6,7], Hebah A. Al-Khatib[6,7], Maria K. Smatti[6,7], Hanan F. Abdul-Rahim[8], Gheyath K. Nasrallah[6,7], Mohamed Ghaith Al-Kuwari[9], Abdullatif Al-Khal[10], Peter Coyle[6,10,11], Imtiaz Gillani[10], Anvar Hassan Kaleeckal[10], Riyazuddin Mohammad Shaik[10], Ali Nizar Latif[10], Einas Al-Kuwari[10], Andrew Jeremijenko[10], Adeel A. Butt[3,10,12], Roberto Bertollini[13], Hamad Eid Al-Romaihi[13], Mohamed H. Al-Thani[13] and Laith J. Abu-Raddad[1,2,3,8*]

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In 2021, Qatar experienced considerable incidence of SARS-CoV-2 infection that was dominated sequentially by the Alpha, Beta, and Delta variants. Using the cycle threshold (Ct) value of an RT-qPCR-positive test to proxy the inverse of infectiousness, we investigated infectiousness of SARS-CoV-2 infections by variant, age, sex, vaccination status, prior infection status, and reason for testing in a random sample of 18,355 RT-qPCR-genotyped infections. Regression analyses were conducted to estimate associations with the Ct value of RT-qPCR-positive tests. Compared to Beta infections, Alpha and Delta infections demonstrated 2.56 higher Ct cycles (95% CI: 2.35-2.78), and 4.92 fewer cycles (95% CI: 4.67- 5.16), respectively. The Ct value declined gradually with age and was especially high for children <10 years of age, signifying lower infectiousness in small children. Children <10 years of age had 2.18 higher Ct

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Original Article

# Duration of immune protection of SARS-CoV-2 natural infection against reinfection

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## Abstract

**Background:** The future of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic hinges on virus evolution and duration of immune protection of natural infection against reinfection. We investigated the duration of protection afforded by natural infection, the effect of viral immune evasion on duration of protection and protection against severe reinfection, in Qatar, between 28 February 2020 and 5 June 2022.

**Methods:** Three national, matched, retrospective cohort studies were conducted to compare the incidence of SARS-CoV-2 infection and coronavirus disease 2019 (COVID-19) severity among unvaccinated persons with a documented SARS-CoV-2 primary infection, to incidence among those infection-naïve and unvaccinated. Associations were estimated using Cox proportional hazard regression models.

**Results:** Effectiveness of pre-Omicron primary infection against pre-Omicron reinfection was 85.5% [95% confidence interval (CI): 84.8–86.2%]. Effectiveness peaked at 90.5% (95% CI: 88.4–92.3%) in the 7th month after the primary infection, but waned to ~70% by the 16th month. Extrapolating this waning trend using a Gompertz curve suggested an effectiveness of 50% in the 22nd month and <10% by the 32nd month. Effectiveness of pre-Omicron primary infection against Omicron reinfection was 38.1% (95% CI: 36.3–39.8%) and declined with time since primary infection. A Gompertz curve suggested an effectiveness of <10% by the 15th month. Effectiveness of primary infection against severe, critical or fatal COVID-19 reinfection was 97.3% (95% CI: 94.9–98.6%), irrespective of the

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# The horizon of pediatric cardiac critical care

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Pediatric Cardiac Critical Care (PCCC) is a challenging discipline where decisions require a high degree of preparation and clinical expertise. In the modern era, outcomes of neonates and children with congenital heart defects have dramatically improved, largely by transformative technologies and an expanding collection of pharmacotherapies. Exponential advances in science and technology are occurring at a breathtaking rate, and applying these advances to the PCCC patient is essential to further advancing the science and practice of the field. In this article, we identified and elaborate on seven key elements within the PCCC that will pave the way for the future.

KEYWORDS

**training, personalized medicine, artificial intelligence, tissue engineering, safety and quality, pediatric cardiac critical care, minimally invasive cardiac surgery, mechanical circulatory support**

## Introduction

In 1671, Neils Stenson described the cardiac pathology of a stillborn fetus with multiple congenital anomalies including the cardiac lesion, which is now recognized as tetralogy of Fallot (1). The first palliative intervention for these patients was pioneered by Hellen Taussig and Alfred Blalock, in November 1944, with the assistance of Vivian Thomas, when the left subclavian artery was anastomosed to the pulmonary artery, with what now known as the Blalock-Thomas-Taussig shunt, in a severely cyanosed child with tetralogy of Fallot (2). A decade later, Sir Walter Lillehei performed the first complete repair for patients with tetralogy of Fallot using human cross-circulation technique (3).

*Original Research*

# Adherence as a Predictor of Glycemic Control Among Adolescents With Type 1 Diabetes: A Retrospective Study Using Real-world Evidence

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## ABSTRACT

**Purpose:** Metabolic control among adolescents with type 1 diabetes mellitus (T1DM) is generally poor. Nonadherence is a contributor to this poor glycemic control, leading to adverse outcomes. The findings of studies reporting the association between adherence and glycemic control are conflicting. This study aimed to assess the level of adherence among adolescents with T1DM and its relationship with glycemic control.

**Methods:** This was a retrospective, cross-sectional study that was conducted at Sidra Medicine, a state-of-the-art tertiary health care facility for women and children in Qatar. Mean blood or interstitial glucose monitoring frequency (BGMF) was used to assess adherence level among adolescents with T1DM, whereas glycemic control was assessed via documented glycated hemoglobin $A_{1c}$ ($HbA_{1c}$). Adolescents who had a mean BGMF of ≥4 checks per day were considered adherent, and those who had an $HbA_{1c}$ level of <7% were considered as having controlled diabetes. Correlational and logistic regression analyses were performed to assess the relationship between adherence and glycemic control, incorporating other covariates into the model.

**Findings:** The rate of adherence among adolescents with T1DM in Qatar was 40.9%. Adherent adolescents had significantly lower median $HbA_{1c}$ levels compared with nonadherent adolescents (9.0% vs. 9.7%; $P = 0.002$). A significant negative correlation was found between BGMF and $HbA_{1c}$ level (correlation coefficient $r_s = -0.325$; $P < .001$). Approximately 97% of nonadherent adolescents compared with 87% of adherent adolescents had suboptimal diabetes control ($HbA_{1c}$ ≥7%) ($P = .016$). Furthermore, nonadherent adolescents were 78% less likely to have controlled diabetes compared with adherent adolescents (adjusted odds ratio = 0.221; 95% CI, 0.063–0.778; $P = 0.019$). The combined effect of the determinants of glycemic control among adolescents with T1DM that were included in the multiple regression model was able to explain approximately 9% of the variances in glycemic control (Cox and Snell $R^2 = 0.092$).

**Implications:** The current findings suggest that nonadherence was highly prevalent among adolescents with T1DM and was a significant independent predictor of glycemic control, explaining 9% of the variability. This finding warrants further exploration of other possible predictors of poor glycemic control among the adolescent population. Comprehensive interventions, including educational, technological, and health service delivery aspects, aimed at improving adherence and ultimately optimizing glycemic control are warranted in adolescents with T1DM. (*Clin Ther.* 2022;44:1380–1392.) 

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# Respiratory virus type to guide predictive enrichment approaches in the management of the first episode of bronchiolitis: A systematic review

Dominika Ambrożej[1,2], Heidi Makrinioti[3], Abigail Whitehouse[4], Nikolas Papadopoulos[5,6], Marek Ruszczyński[7], Aleksander Adamiec[1,2], Jose A. Castro-Rodriguez[8], Khalid Alansari[9,10,11], Tuomas Jartti[12,13,14] and Wojciech Feleszko[1*]

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It has become clear that severe bronchiolitis is a heterogeneous disease; even so, current bronchiolitis management guidelines rely on the one-size-fits-all approach regarding achieving both short-term and chronic outcomes. It has been speculated that the use of molecular markers could guide more effective pharmacological management and achieve the prevention of chronic respiratory sequelae. Existing data suggest that asthma-like treatment (systemic corticosteroids and beta2-agonists) in infants with rhinovirus-induced bronchiolitis is associated with improved short-term and chronic outcomes, but robust data is still lacking. We performed a systematic search of PubMed, Embase, Web of Science, and the Cochrane's Library to identify eligible randomized controlled trials to determine the efficacy of a personalized, virus-dependent application of systemic corticosteroids in children with severe bronchiolitis. Twelve studies with heterogeneous methodology were included. The analysis of the available results comparing the respiratory syncytial virus (RSV)-positive and RSV-negative children did not reveal significant differences in the associatons between systemic

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CASE REPORT

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# A rare presentation of spontaneous rupture of splenic vein aneurysm as cardiac arrest: A case report

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**Abstract**

Splenic vein aneurysm (SVA) is a rare condition associated primarily with portal hypertension. This case highlights a potentially fatal, rare SVA complication in a young patient who presented in cardiac arrest, creating a diagnostic enigma in the emergency department until a POCUS revealed a possible underlying etiology.

**KEYWORDS**

aneurysm, cardiac arrest, spleen, splenic vein rupture

## 1 | INTRODUCTION

Portal vein aneurysms (PVAs) are the most common, yet rarely clinically encountered type of visceral venous aneurysm.[1] PVAs were found in 0.43 percent of the 4186 consecutive patients who underwent routine abdominal contrast-enhanced multidetector computed tomography (MDCT) from 2004 to 2006.[2] These are anatomically classified as intrahepatic or extrahepatic PVAs, with extrahepatic accounting for nearly 63 percent of all cases. Young and old have been equally affected, with an average age of 53.4 years. Aneurysm sizes range from 19 to 50 mm, with a median of 28.4 mm.[2] The majority of aneurysms occur in: The portal vein's main trunk, the hepatic hilus, or the junction of the splenic vein and the superior mesenteric vein.[3] Splenic vein aneurysm first identified in 1953,[4] is a type of extrahepatic PVA.[1,5] SVA can be caused by a congenital weakness in the vessel walls or an acquired cause such as: portal hypertension, liver disease, pancreatitis, or trauma.[1]

Intra-abdominal hemorrhage is a medical emergency that can cause hypovolemic shock, cardiac arrest, and even death if not treated immediately. The most common cause of a life-threatening intra-abdominal bleed is blunt and penetrating abdominal trauma. Nontraumatic causes such as: bleeding from hepatocellular carcinomas, rupture of arterial or venous aneurysms, or spleen rupture are uncommon.[6–9]

We present an intriguing and unusual case of spontaneous rupture of a splenic vein aneurysm, which resulted in hypovolemic shock and cardiac arrest.

## 2 | CASE PRESENTATION

A 19-year-old boy was brought to our emergency department by emergency medical service (EMS) as a case of cardiac arrest. Further history from the family revealed that the patient had been suffering from abdominal pain for the previous 8 h. The pain was sudden in onset and was generalized in location. It was not radiating or shifting anywhere, and there were no reported aggravating or relieving factors. Initially, the pain was milder with no associated symptoms such as: nausea, vomiting, loose stools, constipation, or fever. After nearly 8 h, the pain became more intense, and the patient began to feel dizzy, prompting him to seek medical attention.

The patient was found unconscious with no palpable pulse when the EMS arrived. Cardiopulmonary

ORIGINAL ARTICLES

# Effects of COVID-19 on Pediatric Cancer Care: A Multicenter Study of 11 Middle Eastern Countries

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## Abstract

During the COVID-19 pandemic, major challenges are facing pediatric cancer centers regarding access to cancer centers, continuity of the anti-cancer therapy, hospital admission, and infection protection precautions. Pediatric oncologists actively treating children with cancer from 29 cancer centers at 11 countries were asked to answer a survey from May 2020 to August 2020 either directly or through the internet. COVID-19 pandemic affected the access to pediatric cancer care in the form of difficulty in reaching the center in 22 (75.9%) centers and affection of patients' flow in 21 (72.4%) centers. Health care professionals (HCP) were infected with COVID-19 in 20 (69%) surveyed centers. Eighteen centers (62%) modified the treatment guidelines. Care of follow-up patients was provided in-hospital in 8(27.6%) centers, through telemedicine in 10 (34.5%) centers, and just delayed in 11 (38%) centers. Pediatric oncologists had different expectations about the future effects of COVID-19 on pediatric cancer care. Seventy-six percent of pediatric oncologists think the COVID-19 pandemic will increase the use of telemedicine. Fifty-five percent of pediatric oncologists think if the COVID-19 pandemic persists, we will need to change chemotherapy protocols to less myelosuppressive ones. Collaborative studies are required to prioritize pediatric cancer management during COVID-19 era.

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# Review and Quality Assessment of Systematic Reviews and Meta-analyses on the Management of Pediatric Inguinal Hernias: A Descriptive Study

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ABSTRACT

*Introduction:* Research quality in pediatric surgery has been challenged by multiple factors, including the low incidence of some congenital pathologies and rare event rates. With the rapid increase of pediatric surgical literature, there is a need for systematic reviews to synthesize evidence. It is important to assess the quality of these systematic reviews.
*Objective:* This study aims to examine the reporting of systematic reviews and meta-analyses, using inguinal hernia repair as an index diagnosis.
*Methods:* MEDLINE, Embase, and CINAHL databases were searched for systematic reviews and/or meta-analyses of interventions on inguinal hernia in the pediatric population. The quality reporting was assessed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and A MeaSurement Tool to Assess Systematic Reviews (AMSTAR) 2 tools.
*Results:* Of 1449 unique reports, 21 studies were included (15 meta-analyses and six systematic reviews). Median percent reported items for PRISMA and AMSTAR 2 were 72.2% and 70.5%, respectively. The least reported items in PRISMA were protocol registration (27.6%), synthesis of results (13.0%), and a risk of bias across studies (20.6%). For AMSTAR 2, the least reported items were reporting of source of funding (14.3%), appropriate methods for statistical combination of results (25.0%), and pre-establishment of protocol (28.6%). All critical items were completely or partially fulfilled in 5/21 (23.8%) of the studies and completely absent in 1/21 (4.8%) studies.
*Conclusions:* The results of this study highlight relatively good reporting quality, yet a poor methodological quality of systematic reviews/meta-analyses in the pediatric surgery literature on inguinal hernia management.



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ORIGINAL ARTICLE - CLINICAL SCIENCE

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# Novel technique for transcatheter closure of sinus venosus atrial septal defect: The temporary suture-holding technique

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## Abstract

**Background:** Transcatheter repair of sinus venosus atrial septal defect (SVASD) has become an alternative option to surgical repair. There are potential significant complications related to stent stability in the superior vena cava (SVC) and potential migration of the stent that need to be addressed. Therefore, the technique is still evolving.

**Objectives:** To report results of a new modification "the suture technique" that improves safety profile of positioning and securing a covered stent in the SVC.

**Methods:** This is a descriptive, single center, retrospective review of patients who underwent SVASD closure using the suture technique at our institution between 02/2020 and 08/2022.

**Results:** Fourteen patients underwent transcatheter repair of SVASD using the suture technique. All procedures were successful. The suture technique allowed precise stent placement in all patients without any migration or complication. Six patients required additional stent placement at the level of the SVC. One patient had an additional covered stent placed to eliminate a tiny residual shunt. Two patients had negligible residual shunts at the time of the procedure. At follow-up, all patients clinically improved and had significant reduction in right heart size on echocardiography and/or magnetic resonance imaging. No arrhythmia was reported in any patient. None required re-intervention after a mean follow-up of 16.5 ± *SD* 10.5 months.

**Conclusions:** The suture technique appears to be safe modification. Although our study involves small sample size with no comparative group, we believe our technique offers greater control over stent positioning, reducing the risk of stent embolization and residual shunting in transcatheter closure of SVASD.

KEYWORDS

covered stent, partial anomalous pulmonary venous drainage, sinus venosus atrial septal defect

**Abbreviations:** ASD, atrial septal defect; BMS, bare metal stent; LA, left atrium; LFV, left femoral vein; PA, pulmonary artery; PAPVD, partial anomalous pulmonary venous drainage; RA, right atrium; RFV, right femoral vein; RIJV, right internal jugular vein; RUPV, right upper pulmonary vein; SVASD, sinus venosus ASD; SVC, superior vena cava; TEE, transesophageal echocardiography.

Special Article

# The Middle East and North Africa Diagnosis and Management Guidelines for Inborn Errors of Immunity

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**Human inborn errors of immunity (IEI) are a group of 485 distinct genetic disorders affecting children and adults. Signs and symptoms of IEI are heterogeneous, and accurate diagnosis can be challenging and depends on the available human expertise and laboratory resources. The Middle East and North Africa (MENA) region has an increased prevalence of IEI because of the high rate of consanguinity with a predominance of autosomal recessive disorders. This area also exhibits more severe disease phenotypes compared with other regions, probably due to the delay in diagnosis. The MENA-IEI registry network has designed**

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# Expert Group Consensus on early diagnosis and management of infantile-onset pompe disease in the Gulf Region

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## Abstract

**Background:** Infantile-onset Pompe disease (IOPD) is a rare and devastating, autosomal recessive lysosomal storage disorder that manifests immediately after birth. In severe IOPD cases, complete/almost-complete acid alpha-glucosidase enzyme deficiency is observed. Considering the rapid progression of the disease, timely diagnosis and treatment are important; even slight delays can remarkably alter the course of the disease. Enzyme replacement therapy (ERT) with recombinant human acid alpha-glucosidase is safe and beneficial for IOPD patients. However, there is heterogeneity in the patient response to ERT. The factors influencing treatment effectiveness include the patient's age at the time of treatment initiation, pre-existing muscle damage, and cross-reactive immunologic material (CRIM) status at baseline. Immunomodulation along with ERT is the recently developed therapeutic approach that has been included in the therapeutic armamentarium of IOPD for optimizing clinical benefits, particularly in CRIM-negative IOPD patients. However, there is a dearth of published data on the early diagnosis and clinical position of the immunomodulation protocol along with ERT in the treatment of IOPD in the Gulf region.

**Methods and results:** Expert panel meetings, involving six experts from the Kingdom of Saudi Arabia, Kuwait, Oman, Qatar, and the United Arab Emirates, were convened to develop consensus-based recommendations addressing current diagnostic and management challenges for patients with IOPD in the Gulf region. Furthermore, this consensus guideline may be implemented in clinical practice for the timely diagnosis and management of patients with IOPD.

**Conclusion:** The expert consensus will help clinicians to make appropriate and timely decisions regarding immunomodulation initiation and ERT treatment in IOPD patients in the Gulf region.

**Keywords** Cross-reactive immunologic material status, Enzyme replacement therapy, Gulf countries, Infantile-onset Pompe disease, Immunomodulation protocol

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# Caregiver distress: A mixed methods evaluation of the mental health burden of caring for children with bladder exstrophy

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**Introduction:** Caring for children with bladder exstrophy-epispadias complex (BEEC) exacts a long-term emotional toll on caregivers. Previous studies leave a gap in understanding the impact that caring for a child with BEEC has on caregivers in low- and middle-income countries (LMIC). We hypothesize that families and caregivers experience psychological distress that has long gone unaddressed.

**Materials and methods:** From 2018 to 2020, researchers conducted a multi-method evaluation of caregiver distress with participants recruited as part of the annual International Bladder Exstrophy Collaboration based in Ahmedabad, Gujarat, India. In 2018, pilot data was collected through cognitive interviews. In 2019, researchers conducted structured interviews predicated on themes from the previous year, which subsequently prompted formal mental health screenings in 2020. Caregivers who reported suicidal thoughts were immediately referred for intervention.

**Results:** In 2018, caregivers described the primary source of stigma arose from their village ($n$ = 9, 26.5%). Caregivers also identified long-term concerns ($n$ = 18, 52.9%), including future fertility and marital prospects, as sources of anxiety. In 2019, caregivers substantiated preliminary findings with the primary source of anticipated ($n$ = 9, 31%) and experienced ($n$ = 19, 65.5%) stigma again stemming from their communities. Both cohorts identified the collaboration as a positive source of support ($n$ = 23, 36.5%). In 2020, caregivers stated decreased emotional wellbeing as number of subsequent repairs increased ($n$ = 54, 75%, $p$ = 0.002). Caregivers of children who underwent initial surgery

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Review

# Metabolic changes after surgical fat removal: A dose-response meta-analysis

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Body contouring surgery;
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**Abstract** *Background:* Bariatric surgery averts obesity-induced insulin resistance and the metabolic syndrome. By contrast, surgical fat removal is considered merely an esthetic endeavor. The aim of this article was to establish whether surgical fat removal, similar to bariatric surgery, exerts measurable, lasting metabolic benefits.
*Methods:* PubMed, Embase, and Scopus were searched using the Polyglot Search Translator to find studies examining quantitative expression of metabolic markers. Quality assessment was done using the MethodologicAl STandard for Epidemiological Research scale. The robust-error meta-regression model was employed for this synthesis.
*Results:* Twenty-two studies with 493 participants were included. Insulin sensitivity improved gradually with a maximum reduction in fasting insulin and homeostatic model assessment for insulin resistance of 17 pmol/L and 1 point, respectively, at postoperative day 180. Peak metabolic benefits manifest as a reduction of 2 units in body mass index, 3 kg of fat mass, 5 cm

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# A Multicenter Study Evaluating the Discontinuation of Eculizumab Therapy in Children with Atypical Hemolytic Uremic Syndrome

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**Abstract:** Background: Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening thrombotic microangiopathy (TMA), which has been treated successfully with eculizumab. The optimal duration of eculizumab in treating patients with aHUS remains poorly defined. Methods: We conducted a multicenter retrospective study in the Arabian Gulf region for children of less than 18 years of age who were diagnosed with aHUS and who discontinued eculizumab between June 2013 and June 2021 to assess the rate and risk factors of aHUS recurrence. Results: We analyzed 28 patients with a clinical diagnosis of aHUS who had discontinued eculizumab. The most common reason for the discontinuation of eculizumab was renal and hematological remission (71.4%), followed by negative genetic testing (28.6%). During a median follow-up period of 24 months after discontinuation, 8 patients (28.5%) experienced HUS relapse. The risk factors of recurrence were positive genetic mutations ($p = 0.020$). On the other hand, there was no significant relationship between the relapse and age of presentation, the need for acute dialysis, the duration of eculizumab therapy before discontinuation, or the timing of eculizumab after the presentation. Regarding the renal outcomes after discontinuation, 23 patients were in remission with normal renal function, while 4 patients had chronic kidney disease (CKD) (three of them had pre-existing chronic kidney disease (CKD) before discontinuation, and one case developed a new CKD after discontinuation) and one patient underwent transplantation. Conclusions: The discontinuation of eculizumab in patients with aHUS is not without risk; it can result in HUS recurrence. Eculizumab discontinuation can be performed with close monitoring of the patients. It is essential to assess risk the factors for relapse before eculizumab discontinuation, in particular in children with a positive complement variant and any degree of residual CKD, as HUS relapse may lead to additional loss of kidney function. Resuming eculizumab promptly after relapse is effective in most patients.



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# Quality of life among health care workers in Arab countries 2 years after COVID-19 pandemic

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**Background:** Assessment of the quality of life (QoL) among healthcare workers (HCWs) is vital for better healthcare and is an essential indicator for competent health service delivery. Since the coronavirus disease 2019 (COVID-19) pandemic strike, the frontline position of HCWs subjected them to tremendous mental and psychological burden with a high risk of virus acquisition.

**Aim:** This study evaluated the QoL and its influencing factors among HCWs residing in the Arab countries.

**Methods:** This was a cross-sectional study using a self-administered online questionnaire based on the World Health Organization QoL-BREF instrument with additional questions related to COVID-19. The study was conducted in

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# Acquired Methemoglobinemia in an Infant: Consequence of Prolonged Application of Eutectic Mixture of Local Anesthetics (EMLA) Cream for Spontaneous Abscess Drainage

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## Abstract

Topical anesthetics are commonly used in emergency departments. One of the side effects can be methemoglobinemia if not appropriately used. We present a case of a six-week-old baby who developed methemoglobinemia with levels of 30.6% after prolonged (15 hours) application of Eutectic Mixture of Local Anesthetics (EMLA) cream. The cream was applied for spontaneous drainage of a perianal abscess. The patient received IV methylene blue with a resolution of methemoglobinemia.

**Categories:** Emergency Medicine
**Keywords:** emergency, pediatric, abscess, methemoglobinemia, emla

## Introduction

EMLA (Eutectic Mixture of Local Anesthetics), is a water and oil-based emulsion of 2.5% prilocaine and 2.5% lidocaine [1]. The recommended dose of EMLA in children is 1 gram/10 $cm^2$ of surface area applied for one hour in infants less than three months of age and for four hours in older infants and children [2]. It is commonly used in pediatric emergency departments to achieve local analgesia of intact skin for minor procedures especially intravenous cannulation, spontaneous drainage of a subcutaneous abscess, and lumbar puncture [3-5]. EMLA is a mostly safe topical anesthetic with common side effects such as mild skin reactions in the form of erythema, pallor, edema, and less common systemic side effects in the form of methemoglobinemia, and cardiovascular and central nervous system toxicity [6]. We describe one such case of methemoglobinemia secondary to prolonged application of EMLA cream in an infant. To our knowledge, previously there is no case report of acquired methemoglobinemia secondary to the application of EMLA for abscess drainage.

## Case Presentation

A six-week-old male, previously healthy, was brought to the emergency department in the evening for evaluation of right-sided perianal abscess. As per history, it started as a small papule that gradually increased in size over the next five days with associated erythema and swelling but no discharge. There was no associated fever, difficulty in breathing, vomiting, or diarrhea. On examination, the patient had a 2x2 cm right-sided perianal area of erythema with a central non-draining punctum. Surgery was consulted and the plan was to apply EMLA cream for one hour with the hope of spontaneous drainage of the abscess and to return the next day morning for incision and drainage if there was no spontaneous drainage. Unfortunately, the EMLA was left on the site of the abscess overnight and the next day another dose of EMLA cream was applied. The total application time was 15 hours. The patient had no issues overnight.

The next day, on arrival at the emergency department, vitals were a temperature of 37.6 degree Celsius, respiratory rate of 42 breaths per minute, blood pressure of 86/51 millimeter of mercury, and oxygen saturation of 100% on room air. While awaiting incision and drainage the patient started to have consistent desaturations of 82% on room air with a normal waveform signal on pulse oximetry. At this point, the patient was placed on a 15 L non-rebreather face mask with minimal improvement in oxygen saturation initially. Later oxygen saturation improved to 90% on a 15 L non-rebreather face mask with the respiratory rate ranging between 27-40 breaths per minute. The EMLA cream was removed.

Examination at this point suggested normal heart sounds with no murmurs, normal femoral pulses, and bilateral normal respiratory sounds, no accessory muscle use or cyanosis. There was no family history of methemoglobinemia. Complete cell count (CBC), comprehensive metabolic panel (CMP), venous blood gas (VBG), and glucose 6 phosphate dehydrogenase (G6PD) levels were sent to the laboratory. EKG suggested normal sinus rhythm, with no hypertrophy and axis deviation. An X-ray chest suggested a normal cardiopulmonary silhouette. The VBG revealed a methemoglobin level of 30.6%, with the rest of the values unremarkable. CBC showed a hemoglobin level of 10.1 g/dl and CMP was normal. While waiting for G6PD levels, VBG was repeated in three hours which showed a methemoglobin level of 26.4%. After normal G6PD

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# Dietary long-chain omega 3 fatty acids modify sphingolipid metabolism to facilitate airway hyperreactivity

Andrea Heras[1,7], Rika Gomi[1,7], Madeline Young[1,7], Chuchun L. Chang[2], Emily Wasserman[1,3], Anurag Sharma[1], Wenzhu Wu[1], Jinghua Gu[3], Uthra Balaji[3], Rachel White[1], Perdita Permaul[1], Ibrahim Janahi[4], Tilla S. Worgall[5,7] & Stefan Worgall[1,3,6,7]✉

**Omega-3 polyunsaturated fatty acids (n-3 PUFAs) are essential nutrients that can affect inflammatory responses. While n-3 PUFAs are generally considered beneficial for cardiovascular disease and obesity, the effects on asthma, the most common inflammatory lung disease are unclear. While prenatal dietary n-3 PUFAs decrease the risk for childhood wheezing, postnatal dietary n-3 PUFAs can worsen allergic airway inflammation. Sphingolipid metabolism is also affected by dietary n-3 PUFAs. Decreased sphingolipid synthesis leads to airway hyperreactivity, besides inflammation, a cardinal feature of asthma, and common genetic asthma risk alleles lead to lower sphingolipid synthesis. We investigated the effect of dietary n-3 PUFAs on sphingolipid metabolism and airway reactivity. Comparing a fish-oil diet with a high n-3 PUFA content (FO) to an isocaloric coconut oil-enriched diet (CO), we found an n-3 PUFA-dependent effect on increased airway reactivity, that was not accompanied by inflammation. Lung and whole blood content of dihydroceramides, ceramides, sphingomyelins, and glucosylceramides were lower in mice fed the n-3 PUFA enriched diet consistent with lower sphingolipid synthesis. In contrast, phosphorylated long chain bases such as sphingosine 1-phosphate were increased. These findings suggest that dietary n-3 PUFAs affect pulmonary sphingolipid composition to favor innate airway hyperreactivity, independent of inflammation, and point to an important role of n-3 PUFAs in sphingolipid metabolism.**

Polyunsaturated fatty acids (PUFAs), essential nutrients with a multitude of biological effects mainly related to growth and metabolism, are actively incorporated as acyl chains into cell membrane lipids, including sphingolipids, and can affect membrane scaffold formation, energy storage and signal transduction by lipid mediators[1]. N-3 PUFAs have anti-inflammatory effects[2] which attenuate systemic inflammation associated with obesity and cardiovascular disease[3,4]. N-3 PUFAs may also be beneficial in asthma as: (1) Exhaled breath condensates of asthmatic individuals contained lower levels of a n-3 PUFA docosahexaenoic acid derivative[5]; and decreased airway reactivity inflammation with allergic sensitization can be achieved (2) by oral or aerosolized administration n-3 PUFAs or derivatives[5–10]; and (3) by endogenously increasing n-3 PUFAs in transgenic mice expressing a n-3 fatty acid desaturase[11]. In contrast, exacerbation of inflammation by n-3 PUFAs has been seen with allergic airway and intestinal inflammation[12–14] and infection[15–17] models.

Polymorphisms within the 17q21 chromosomal region that increase expression of the sphingolipid synthesis inhibitor ORMDL3 are linked to childhood asthma[18–20] and obesity[21]. ORMDL3 inhibits serine palmitoyl transferase (SPT), the rate-limiting enzyme in de novo sphingolipid synthesis[22,23]. ORMDL3-overexpressing mice as well as knockdown or pharmacological inhibition of SPT lead to decreased lung sphingolipid levels and innate airway hyperreactivity[24,25]. We investigated the effects of n-3 PUFAs on sphingolipid metabolism and airway

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# Protection from previous natural infection compared with mRNA vaccination against SARS-CoV-2 infection and severe COVID-19 in Qatar: a retrospective cohort study

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## Summary

**Background** Understanding protection conferred by natural SARS-CoV-2 infection versus COVID-19 vaccination is important for informing vaccine mandate decisions. We compared protection conferred by natural infection versus that from the BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna) vaccines in Qatar.

**Methods** We conducted two matched retrospective cohort studies that emulated target trials. Data were obtained from the national federated databases for COVID-19 vaccination, SARS-CoV-2 testing, and COVID-19-related hospitalisation and death between Feb 28, 2020 (pandemic onset in Qatar) and May 12, 2022. We matched individuals with a documented primary infection and no vaccination record (natural infection cohort) with individuals who had received two doses (primary series) of the same vaccine (BNT162b2-vaccinated or mRNA-1273-vaccinated cohorts) at the start of follow-up (90 days after the primary infection). Individuals were exact matched (1:1) by sex, 10-year age group, nationality, comorbidity count, and timing of primary infection or first-dose vaccination. Incidence of SARS-CoV-2 infection and COVID-19-related hospitalisation and death in the natural infection cohorts was compared with incidence in the vaccinated cohorts, using Cox proportional hazards regression models with adjustment for matching factors.

**Findings** Between Jan 5, 2021 (date of second-dose vaccine roll-out) and May 12, 2022, 104500 individuals vaccinated with BNT162b2 and 61955 individuals vaccinated with mRNA-1273 were matched to unvaccinated individuals with a documented primary infection. During follow-up, 7123 SARS-CoV-2 infections were recorded in the BNT162b2-vaccinated cohort and 3583 reinfections were recorded in the matched natural infection cohort. 4282 SARS-CoV-2 infections were recorded in the mRNA-1273-vaccinated cohort and 2301 reinfections were recorded in the matched natural infection cohort. The overall adjusted hazard ratio (HR) for SARS-CoV-2 infection was 0·47 (95% CI 0·45–0·48) after previous natural infection versus BNT162b2 vaccination, and 0·51 (0·49–0·54) after previous natural infection versus mRNA-1273 vaccination. The overall adjusted HR for severe (acute care hospitalisations), critical (intensive care unit hospitalisations), or fatal COVID-19 cases was 0·24 (0·08–0·72) after previous natural infection versus BNT162b2 vaccination, and 0·24 (0·05–1·19) after previous natural infection versus mRNA-1273 vaccination. Severe, critical, or fatal COVID-19 was rare in both the natural infection and vaccinated cohorts.

**Interpretation** Previous natural infection was associated with lower incidence of SARS-CoV-2 infection, regardless of the variant, than mRNA primary-series vaccination. Vaccination remains the safest and most optimal tool for protecting against infection and COVID-19-related hospitalisation and death, irrespective of previous infection status.

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## Introduction

COVID-19 vaccines induce protection against SARS-CoV-2 infection and COVID-19-related hospitalisation and death.[1–4] Natural infection with SARS-CoV-2 also induces protection against subsequent SARS-CoV-2 infection and COVID-19-related hospitalisation and death.[5,6] An increasing number of studies suggest that differences exist in the level and durability of protection conferred by natural infection versus vaccination.[7–11] This variation might arise from differences in several factors, including the mechanism of action,[12,13] mucosal immunity,[14,15] the volume and nature of neutralising antibody titres,[12,16,17] and circulating variants.[18–22]

Understanding protection conferred by natural SARS-CoV-2 infection versus COVID-19 vaccination is important for informing vaccine mandate decisions.

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# Clinical, immunological, molecular and therapeutic findings in monogenic immune dysregulation diseases: Middle East and North Africa registry

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*Abbreviations:* AIHA, Autoimmune hemolytic anemia; CBC, Complete cell blood count; CD, Cluster of differentiation; CID, Combined immunodeficiency; CMV, Cytomegalovirus; COVID-19, Coronavirus disease; CTLA-4, Cytotoxic T-lymphocyte-associated protein 4; CVID, Common variable immunodeficiency; DNT, Double negative T; EBV, Epstein-Barr virus; ESID, European Society for Immunodeficiencies; GOF, Gain of function; GvHD, Graft-versus-host-disease; HLH, Hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplantation; IBD, Inflammatory bowel disease; IEI, Inborn error of immunity; Ig, Immunoglobulin; IL, Interleukin; IQR, Interquartile range; ITP, idiopathic thrombocytopenic purpura; IUIS, International Union of Immunological Societies; IgRT, immunoglobulin replacement therapy; JAK, Janus kinase; LRBA, LPS Responsive Beige-Like Anchor; MENA, Middle East and North Africa; MIDD, Monogenic immune dysregulation diseases; NK, Natural killer; RTI, Respiratory tract infection; STAT, Signal transducer and activator of transcription; Th, T helper; Tregs, Regulatory T cells.

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ORIGINAL ARTICLE

# Covid-19 Vaccine Protection among Children and Adolescents in Qatar

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## ABSTRACT

### BACKGROUND

The BNT162b2 vaccine against coronavirus disease 2019 (Covid-19) has been authorized for use in children 5 to 11 years of age and adolescents 12 to 17 years of age but in different antigen doses.

### METHODS

We assessed the real-world effectiveness of the BNT162b2 vaccine against infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) among children and adolescents in Qatar. To compare the incidence of SARS-CoV-2 infection in the national cohort of vaccinated participants with the incidence in the national cohort of unvaccinated participants, we conducted three matched, retrospective, target-trial, cohort studies — one assessing data obtained from children 5 to 11 years of age after the B.1.1.529 (omicron) variant became prevalent and two assessing data from adolescents 12 to 17 years of age before the emergence of the omicron variant (pre-omicron study) and after the omicron variant became prevalent. Associations were estimated with the use of Cox proportional-hazards regression models.

### RESULTS

Among children, the overall effectiveness of the 10-$\mu$g primary vaccine series against infection with the omicron variant was 25.7% (95% confidence interval [CI], 10.0 to 38.6). Effectiveness was highest (49.6%; 95% CI, 28.5 to 64.5) right after receipt of the second dose but waned rapidly thereafter and was negligible after 3 months. Effectiveness was 46.3% (95% CI, 21.5 to 63.3) among children 5 to 7 years of age and 16.6% (95% CI, −4.2 to 33.2) among those 8 to 11 years of age. Among adolescents, the overall effectiveness of the 30-$\mu$g primary vaccine series against infection with the omicron variant was 30.6% (95% CI, 26.9 to 34.1), but many adolescents had been vaccinated months earlier. Effectiveness waned over time since receipt of the second dose. Effectiveness was 35.6% (95% CI, 31.2 to 39.6) among adolescents 12 to 14 years of age and 20.9% (95% CI, 13.8 to 27.4) among those 15 to 17 years of age. In the pre-omicron study, the overall effectiveness of the 30-$\mu$g primary vaccine series against SARS-CoV-2 infection among adolescents was 87.6% (95% CI, 84.0 to 90.4) and waned relatively slowly after receipt of the second dose.

### CONCLUSIONS

Vaccination in children was associated with modest, rapidly waning protection against omicron infection. Vaccination in adolescents was associated with stronger, more durable protection, perhaps because of the larger antigen dose. (Funded by Weill Cornell Medicine–Qatar and others.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Chemaitelly can be contacted at hsc2001@qatar-med.cornell.edu. Dr. Abu-Raddad can be contacted at lja2002@qatar-med.cornell.edu. Drs. Chemaitelly and Abu-Raddad can also be contacted at the Infectious Disease Epidemiology Group, Weill Cornell Medicine–Qatar, Qatar Foundation–Education City, P.O. Box 24144, Doha, Qatar.

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BMC Infectious Diseases

RESEARCH Open Access

# Microbiological and clinical characteristics of invasive Group B Streptococcal blood stream infections in children and adults from Qatar

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## Abstract

**Introduction:** *Group B Streptococci* (GBS) colonize almost one third of human gastrointestinal and genitourinary tracts, particularly in females. The aim of this study is to evaluate the epidemiology, microbiological characteristics, and clinical outcomes of invasive GBS disease in Qatar from all age groups.

**Methods:** A retrospective study was conducted on patients with confirmed GBS blood stream infections during the period between January 2015 and March 2019. Microbiological identification was performed using automated BD PhoenixTM system, while additional antimicrobial susceptibility tests were performed using E test and disc diffusion methods.

**Result:** During the four years period, the incidence steadily rose from 1.48 to 2.09 cases per 100.000 population. Out of 196 confirmed cases of invasive GBS infections, the majority were females (63.7%, 125/196) of which 44.8% were pregnant and 53.6% were colonized. Three distinct affected age groups were identified: children ≤ 4 years of age (35.7%), young adults 25–34 (20.9%) and the elderly ≥ 65 year (17.4%). Presenting symptoms were mild with fever in 53% of cases while 89% of cases had Pitt bacteraemia score of ≤ 2. Isolates were universally sensitive to penicillin, ceftriaxone, and vancomycin at 100% but with significant resistance to erythromycin (49%) and clindamycin (28.6%) while 16.8% had inducible clindamycin resistance. Clinical outcomes showed cure rate of 87.25% with complications in (8.76%) and 4% mortality.

**Conclusion:** There is a rising trend of Group B Streptococcal blood stream infections in Qatar with significantly high clindamycin and erythromycin resistance rates. Universal susceptibility rates were demonstrated for penicillin, ceftriaxone, and vancomycin.

**Keywords:** Group B Streptococci (GBS), Strep agalactiae, Sepsis, Bacteraemia, Qatar

## Introduction

*Group B Streptococci* (GBS) are gram-positive cocci that commonly colonize the gastrointestinal and genitourinary tracts of adults particularly of females and pregnant women [1]. Despite being harmless in the majority of colonized individuals, the pathogen is capable of causing invasive diseases primarily in neonates, infants, pregnant and postpartum women as well as the elderly with significant morbidity and mortality [2].

The spectrum of the invasive disease including maternal and neonatal sepsis, was recognised during the 1960s which led to major public health measures to improve recognition, management and prevention of GBS

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# Post-COVID mRNA vaccine myocarditis in children: report of two cases

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## SUMMARY

The SARS-COV-2 pandemic led to the development of several vaccinations to contain the disease. The Pfizer-BioNTech COVID-19 (BNT162b2) vaccine was recommended on May 2021 for use in children above 12 years and older. The vaccine is safe, well tolerated and highly effective. Initial reports showed no serious adverse events; however, cases of myocarditis in young healthy male adolescents have been reported. We report two cases of myocarditis/perimyocarditis who presented with short history of chest pain following administration of the second dose of the MRN COVID-19 vaccine.

## BACKGROUND

Although post-COVID-19 vaccination myocarditis is rare, it is a known side effect of the vaccine.[1] Studies from the USA show that the risk of myocarditis after receiving mRNA-based COVID-19 vaccines is increased across all age and sex groups. Epidemiological studies reported an incidence of 20–30 per million patients, and the risk is highest after the second vaccination dose in adolescent males.[2 3] The Centers for Disease Control and Prevention (CDC) recommends that COVID-19 primary series vaccines should be given to everyone aged 6 months and older with COVID-19 boosters for everyone 5 years and older.[4] The vaccine shows excellent efficacy and safety outcomes, but the long-term side effects are still under investigations.[5] We report two adolescent males who developed acute myocarditis, post Pfizer-BioNTech vaccine for COVID-19. The healthcare provider is to suspect myocarditis in healthy children who recently received COVID-19 vaccinations and presented with chest pain with or without cardiac symptoms.

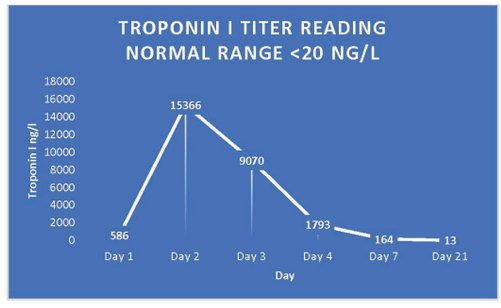


**Figure 1** Case 1: troponin I titre reading recorded over 3 weeks.

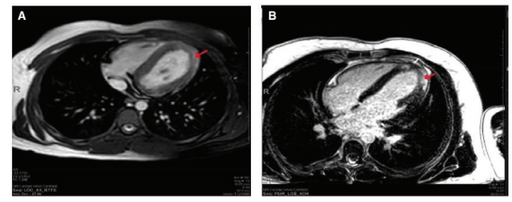


**Figure 2** Case 1: Cardiac MRI (A) long axis view showing an abnormal high signal intensity of myocardium highlighted by the arrows. (B) four-chamber views post gadolinium showing late gadolinium enhancement.

## CASE PRESENTATION

### Case 1

A boy in early adolescence with no significant medical history, apart from Perthe's disease. He presented with a 1-day history of chest pain radiating to the left arm. There were no other symptoms. He received the second Pfizer-BioNTech vaccine dose 4 days before presentation to the paediatric emergency department (PED). On arrival, all his vital signs vitals were stable. His aural temperature was 37°C, heart rate was: 67 beats per minute (bpm), respiratory rate (RR) was 16 bpm, blood pressure was 126/59 mm Hg and oxygen saturation - SpO2 was 100% in air. His weight was 71 kg (90th centile), height was 165 cm (25th centile) and body mass index (BMI) 26.1 kg/m$^2$. Serum troponin I level, on arrival to PED, was raised at 586 ng/L (normal values <20 ng/L) (see figure 1). ECG showed diffuse ST segment changes and cardiacecho was normal with left ventricular ejection fraction of 67%. The cardiac MRI (cMRI) showed myocardial oedema, wall motion abnormality and transmural delayed enhancement at the apical lateral region of left ventricle supporting the diagnosis of myocarditis (figure 2). His COVID-19 nasal swab antigen test was negative; however, his COVID-19 IgG antibodies were positive with a titre of (binding antibody units -BAU)1930 BAU/mL. He was admitted to paediatric intensive care unit (PICU) for close monitoring of his clinical condition and serum troponin levels (figure 1). He received intravenous immunoglobulin, but this was stopped soon after been started as he developed severe chest pain.

### Case 2

A boy in early adolescence with a medical history of allergic rhinitis, presented with 1-day history of non-radiating central chest pain. He had no other symptoms. He had received the second Pfizer-BioNTech vaccine 5 days before attending the PED.



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CANCER THERAPY AND PREVENTION

IJC INTERNATIONAL JOURNAL of CANCER

# Outcomes of patients with Wilms' tumour stage III due to positive resection margins only: An analysis of patients treated on the SIOP-WT-2001 protocol in the UK-CCLG and GPOH studies

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## Abstract

Stage III Wilms' tumour (WT) represents a heterogeneous group which includes different criteria, but all stage III patients are treated according to the same study regiment. The aim of the study was to retrospectively analyse outcomes in patients with stage III due to positive resection margins (RM) only, sub-grouped in RM with viable (RM-v) and nonviable (RM-nv) tumour. Patients were treated pre- and postoperatively according to the SIOP-WT-2001 protocol in the UK-CCLG and GPOH WT trials and studies (2001-2020). There were 197 patients, including 134 with localised, abdominal stage III and 63 with overall stage IV, but abdominal stage III. Stage III due to RM-v had 126 patients, and due to RM-nv 71 patients. The overall 5-year local-relapse-free survival (RFS), event-free (EFS) and overall survival (OS) estimates for all patients with abdominal stage III RM were 95.7% (±SE1.5%), 85.1 (±SE2.6%) and 90.3% (±SE2.2%), respectively. Patients with stage III RM-nv had significantly better

**Abbreviations:** AIEOP, Associazione Italiana di Ematologia e Oncologia Pediatrica; CCLG, Children's Cancer and Leukaemia Group; CIC, chemotherapy-induced changes; COG, Children's Oncology Group; EFS, event-free survival; GPOH, Gesellschaft für Pädiatrische Onkologie und Hämatologie; HR-WT, high-risk Wilms' tumour; IMPORT, Improving Population Outcomes for Renal Tumours of Childhood; IR-WT, intermediate-risk Wilms' tumour; LR-WT, low-risk Wilms' tumour; NWTS, National Wilms Tumour Study; OS, overall survival; RFS, relapse free survival; RM, resection margin; SIOP, International Society of Paediatric Oncology; WT, Wilms' tumour.

Gordan M. Vujanić and Rhoikos Furtwängler contributed equally to the article.

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Review

# Metabolic changes after nonsurgical fat removal: A dose response meta-analysis

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**KEYWORDS**
Cryolipolysis;
Laser lipolysis;
Radiofrequency ablation;
High intensity focused thermal ultrasound (HIFU);
BMI;
Lipid profile

**Summary** *Background:* Obesity-induced insulin resistance leads to the metabolic syndrome. Both bariatric surgery and surgical fat removal have been shown to improve metabolic health, but the metabolic benefits of nonsurgical fat removal remain uncertain. The aim of this paper is to establish whether nonsurgical fat removal exerts measurable, lasting metabolic benefits by way of changes to serum lipid profiles.
*Methods:* PubMed, Cochrane CENTRAL, Embase, and clinical trials registers were searched using the Polyglot Search Translator to find studies examining quantitative changes in metabolic markers after nonsurgical body contouring procedures. The MethodologicAl STandard for Epidemiological Research (MASTER) scale was adopted for the quality assessment of the included studies. The robust-error meta-regression (REMR) model was employed.
*Results:* Twenty-two studies and 676 participants were included. Peak body compositions measures manifest as a reduction of 2 units in body mass index (BMI), 1 kg of body weight (BW), 5 cm in waist circumference (WC) and 1.5 cm in abdominal fat thickness (FT), sustained up to 60 days postprocedure. Transient increases of 15 mg/dL in low-density lipoprotein (LDL), 10 mg/dl in triglycerides (TG), and 15 mg/dl in total cholesterol (TC) were observed at 2 weeks postprocedure.

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ORIGINAL ARTICLE

WILEY

# Predictors of early death risk among untransplanted patients with combined immunodeficiencies affecting cellular and humoral immunity: A multicenter report

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## Abstract

**Background:** There is an increased demand for hematopoietic stem cell transplant (HSCT) to treat various diseases including combined immunodeficiencies (CID), with limited worldwide availability. Variables affecting the decision regarding CID patients' prioritization for HSCT are not known. We aimed to determine general, clinical, and immunologic factors associated with the higher risk of early death (≤6 months after diagnosis) in untransplanted CID patients.

**Methods:** Data collection was done retrospectively from five centers and included general patients' information, and clinical and laboratory variables. Inclusion criteria were untransplanted patients who are either dead or alive with a follow-up period ≥6 months after diagnosis.

**Results:** Two hundred and thirty-six CID patients were reported by participating centers, of whom 111 were included in the study with a cumulative follow-up period of 278.6 years. Seventy-two patients died with the median age of death of 10.5 months. 35.1% of the patients succumbed within 6 months after the diagnosis. Having a history of *Candida* infections, sepsis or hepatomegaly was associated with an increased risk of early death. None of the other general or clinical variables was associated with such risk. Bivariate analysis of lymphocyte subsets showed that patients with the following counts: $CD3^+ < 100$, $CD4^+ < 200$, $CD8^+ < 50$, or $CD16^+CD56^+ < 200$ cells/μl had increased risk of early death. In adjusted analysis, increased risk of early death was observed among patients with $CD3^+$ count <100 cells/μl.

**Conclusion:** Combined immunodeficiencies patients with a history of *Candida* infections, sepsis, hepatomegaly, or severe T-lymphopenia should be given priority for HSCT to avoid early death.

**Abbreviations:** ADA, adenosine deaminase; AK2, adenylate kinase 2; CI, confidence interval; CID, combined immunodeficiencies affecting cellular and humoral immunity; DOCK8, dedicator of cytokinesis 8; HR, hazard ratio; HSCT, hematopoietic stems cell transplant; IQR, interquartile range; KM, Kaplan–Meier; MHC II, major histocompatibility II; SCID, severe combined immunodeficiency.

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# Addressing violence against children: A case review in the state of Qatar

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**Introduction:** Violence against children (VAC) is a critical public health issue that affects billions of children worldwide. The combination of its prevalence and severity of effects on children creates an urgent need for effective interventions. Multiple studies associate VAC with lifelong implications that affect children through adulthood. In Qatar, multiple approaches such as legislation are being used to protect children from all forms of violence. Despite the gravity of the issue, there is still low readiness for the prevention of VAC in Qatar. This review aimed to map approaches to addressing VAC in Qatar from the panelists' perspectives on current approaches to addressing VAC.

**Methods:** The review obtained data from a recorded video entitled "A Public Health Approach to Addressing Violence Against Children." The panel discussion in this video clip was organized as a side event of the WISH virtual summit by UNICEF and WISH on World Children's Day, held in Qatar in November 2020. The video was transcribed and analyzed using thematic analysis.

**Findings:** It shows the importance of both global and national level interventions in addressing VAC. The review uses the socioecological model to show relationships among different levels of interventions addressing VAC in Qatar. The findings highlight the national approaches to addressing VAC using public health, and legislative and policy approaches.

**Discussion:** The interventions addressing VAC at different levels in Qatar are interconnected. Delineating each level is key to the formation of holistic interventions that leverage global, regional, national, communal, familial, and individual factors that support interventions to address VAC.

KEYWORDS

**Child health, Child Abuse, public health, violence against children, thematic analysis, socioecological model**

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ORIGINAL ARTICLE

WILEY

# Intraoperative cytological diagnosis of brain tumours: A preliminary study using a deep learning model

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## Abstract

**Background:** Intraoperative pathological diagnosis of central nervous system (CNS) tumours is essential to planning patient management in neuro-oncology. Frozen section slides and cytological preparations provide architectural and cellular information that is analysed by pathologists to reach an intraoperative diagnosis. Progress in the fields of artificial intelligence and machine learning means that AI systems have significant potential for the provision of highly accurate real-time diagnosis in cytopathology.

**Objective:** To investigate the efficiency of machine-learning models in the intraoperative cytological diagnosis of CNS tumours.

**Materials and Methods:** We trained a deep neural network to classify biopsy material for intraoperative tissue diagnosis of four major brain lesions. Overall, 205 medical images were obtained from squash smear slides of histologically correlated cases, with 18 high-grade and 11 low-grade gliomas, 17 metastatic carcinomas, and 9 non-neoplastic pathological brain tissue samples. The neural network model was trained and evaluated using 5-fold cross-validation.

**Results:** The model achieved 95% and 97% diagnostic accuracy in the patch-level classification and patient-level classification tasks, respectively.

**Conclusions:** We conclude that deep learning-based classification of cytological preparations may be a promising complementary method for the rapid and accurate intraoperative diagnosis of CNS tumours.

KEYWORDS
artificial intelligence, brain tumour, cytopathology, deep learning, intraoperative diagnosis, neural networks

## 1 | INTRODUCTION

The central nervous system (CNS) is the most common site of cancer in children and adolescents. Although CNS tumours are not the leading cancer type in adults, over half of brain cancers are metastatic carcinomas that originate elsewhere in the body, and gliomas are the most common primary tumours.[1] The gold standard for determination of a final diagnosis of a brain tumour is the microscopic examination of biopsy material by a neuropathologist. Neurosurgeons typically send a piece of lesional tissue for an expedited intraoperative consultation at which the next surgical step is decided; this could either be the cessation of surgery or the pursuit of aggressive surgical resection. In addition, accurate intraoperative pathological diagnosis of CNS tumours is essential for patient management and may help to make decisions regarding the intraoperative use of radiation therapy or adjuvant chemotherapy during surgery for high-grade glial tumours.[2,3]

The intraoperative microscopic diagnosis of brain biopsies can be made by examining frozen sections (FSs) and cytology preparations.

  

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*Research Article*

# Outcome of Newborns with Tracheoesophageal Fistula: An Experience from a Rapidly Developing Country: Room for Improvement

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*Introduction/Purpose*. Tracheoesophageal fistula (TEF) represents one of the most common congenital developmental malformations of the upper digestive tract. The optimal surgical management has several controversies, particularly in rapidly developing countries. Morbidity and mortality are highly variable between centers and are dependent on various factors. However, complex medical care has considerably improved, especially in developing countries. This study describes the experience of our center in patients with TEF with emphasis on the clinical characteristics, postoperative immediate and long-term respiratory and gastrointestinal complications, and the mortality rate of such cases which would allow us to compare our results with other regional pediatric tertiary centers. *Methods*. This is a retrospective review of the medical electronic charts of patients with TEF that were followed at Sidra Medicine in the state of Qatar. The review included the patients who were operated upon in the period of 2011-2021 but continued to follow at our institution in the period of 2018-2021. Demographic data, associated anomalies, preoperative, operative, and postoperative courses, and growth parameters were collected. *Results*. A total of 35 patients with TEF (24 males and 11 females) were collected. 49% were full term. We identified seven patients (20%) with isolated TEF, TEF with VACTERL association in 29% of our patients, other chromosomal anomalies in 17%, or associated with other anomalies (not related to VACTERL) in 34% of the patients. The majority of the patients (94%) were of type C-TEF (TEF with esophageal atresia–EA/TEF). All patients were operated except for one patient who died at 2 days of life due to cardiac complications. Median age at which surgery was performed was 2 days (range 1-270 days). Median follow-up was 32 months (range 7-115 months). Immediate postoperative complications were encountered in eleven patients (33%) and included anastomosis leak in 12%, air leak in 6%, sepsis in 6%, chylothorax in 3%, vocal cord palsy and fistula recurrence (combined) in 3%, and failure of TEF closure in 3% of the patients. Long-term respiratory complications were encountered in 43% of our patients. Long-term gastrointestinal complications included gastroesophageal reflux (GERD) in 63%, dysphagia in 31%, and anastomotic stricture in 34% of the patients. Growth was affected in around a quarter of the patients at 6 months after surgery and 22% at 12-month assessment postoperatively. While only five patients died at our institution, only one was directly related to failure of TEF closure and postoperative complications. *Conclusion*. This descriptive study reports the clinical outcome of TEF from a rapidly developing country. The distribution of the patients' characteristics and postoperative complications was almost comparable to those from developed countries. This study would aid in addressing the prognostic factors and establishment of evidence-based management pathways of newborns with TEF to improve the clinical outcome in our center and other pediatric tertiary centers in developing countries.

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ORIGINAL ARTICLE

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# A breakthrough effect of gene replacement therapy on respiratory outcomes in children with spinal muscular atrophy

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## Abstract

**Introduction:** Spinal muscular atrophy (SMA) is an inherited progressive neuromuscular disorder characterized by generalized hypotonia, respiratory failure and early death. The introduction of gene replacement therapy (GRT) modified the natural history of the disease. However, more data is needed to understand the long-term effect of GRT on measurable respiratory outcomes. We report the respiratory outcomes in our cohort of patients with SMA post-GRT in 2-year period.

**Methods:** A retrospective chart-review of genetically confirmed children with SMA who received GRT between 2019 and 2021 in Qatar. The evaluated respiratory outcomes were chronic respiratory support, respiratory hospitalizations, escalation of respiratory support and polysomnography results before and after GRT. Nonrespiratory outcomes; nutritional status, swallowing, and motor functions; were also assessed.

**Results:** A total of 11 patients (9 patients with SMA-1 and 2 patients with SMA-2) received GRT at a median age of 12 months and 22 months in patients with SMA-1 and SMA-2, respectively. All patients were successfully weaned off Noninvasive ventilation (NIV) except one patient who remained on mechanical ventilation through tracheostomy tube. The annualized hospitalization rate dropped by half after GRT. The average length of stay (LOS) in intensive care unit (ICU) decreased by 17.32 days/patient/year after GRT. Duration of required escalation of respiratory support during acute hospitalizations has dropped by 18.56 days/patient/year post-GRT.

**Conclusion:** We report favorable respiratory outcomes of GRT in our cohort. GRT resulted in discontinuation of chronic respiratory support in majority of ventilated patients. GRT also resulted in decreased respiratory hospitalization rate, hospital-LOS, ICU-LOS, and need for escalation of ventilatory support.

KEYWORDS

gene replacement therapy, onasemnogene abeparvovec, respiratory outcome, spinal muscular atrophy

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SPECIAL REPORT

# The varied spectrum of nephroblastomatosis, nephrogenic rests, and Wilms tumors: Review of current definitions and challenges of the field

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## Abstract

The diagnosis of multiple or diffuse renal lesions in a child is challenging by imaging and/or pathology. Optimal management requires distinguishing benign lesions such as nephrogenic rests from cancerous lesions such as Wilms tumor, but this is often difficult or impossible. This difficulty is compounded by the overlapping nature of our current radiologic and pathologic definitions of lesions along the spectrum of nephrogenic rests/nephroblastomatosis. We provide a review of these issues, as a collaborative effort between the Children's Oncology Group Renal Tumor Committee and International Society of Pediatric Oncology Renal Tumor Study Group. Our aim is to discuss current challenges in diagnosis and management of these renal lesions, encouraging future work toward consensus definitions for research and patient care.

KEYWORDS
nephroblastomatosis, nephrogenic rests, Wilms tumors

**Abbreviations:** COG, Children's Oncology Group; CT, computed tomography; DHPLN, diffuse hyperplastic perilobar nephroblastomatosis; HPLN, hyperplastic perilobar nephroblastomatosis; ILNR, intralobar nephrogenic rest; MRI, magnetic resonance imaging; NR, nephrogenic rest; NSS, nephron sparing surgery; PLNR, perilobar nephrogenic rest; RA, retinoic acid; RTSG, Renal Tumor Study Group; SIOP, International Society of Pediatric Oncology; US, ultrasound; WT, Wilms tumor.

Rhoikos Furtwaengler and Elizabeth Mullen contributed equally as senior authors.

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Article

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# Cross-kingdom synthetic microbiota supports tomato suppression of Fusarium wilt disease

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Check for updates

Xin Zhou[1,2], Jinting Wang[1,2], Fang Liu[1], Junmin Liang[1], Peng Zhao[1], Clement K. M. Tsui[3,4,5,6] & Lei Cai[1,2]

The role of rhizosphere microbiota in the resistance of tomato plant against soil-borne Fusarium wilt disease (FWD) remains unclear. Here, we showed that the FWD incidence was significantly negatively correlated with the diversity of both rhizosphere bacterial and fungal communities. Using the microbiological culturomic approach, we selected 205 unique strains to construct different synthetic communities (SynComs), which were inoculated into germ-free tomato seedlings, and their roles in suppressing FWD were monitored using omics approach. Cross-kingdom (fungi and bacteria) SynComs were most effective in suppressing FWD than those of Fungal or Bacterial SynComs alone. This effect was underpinned by a combination of molecular mechanisms related to plant immunity and microbial interactions contributed by the bacterial and fungal communities. This study provides new insight into the dynamics of microbiota in pathogen suppression and host immunity interactions. Also, the formulation and manipulation of SynComs for functional complementation constitute a beneficial strategy in controlling soil-borne disease.

Tomato (*Solanum lycopersicum*) is one of the most widely grown vegetable worldwide, and the increasing market demand is met by large-scale greenhouse cultivation. Owning to the widespread application of agrochemicals and monoculture farming, outbreaks of fungal diseases, such as wilt disease caused by *Fusarium oxysporum* f. sp. *lycopersici* (*FOL*), have been frequently reported. Fusarium wilt disease (FWD) has become one of the most significant diseases leading to tomato yield losses, and its prevention and control have become a global concern[1,2]. In China, the increased incidence of FWD in the greenhouse has severely impacted the development of tomato industry. Chemical fungicides and soil fumigation have been widely used for controlling FWD disease. These methods, however, have been criticized as they pose threats to human health and cause environmental pollution. Also, the long-term application of chemicals upsets the balance of the soil micro-ecological environment and destroys the natural "probiotic" microbiota, thus aggravating the occurrence of tomato wilt disease[3,4]. The development of novel and environmental friendly approaches are essential to reduce the FWD incidence and yield loss in tomato.

Plant-associated microbes play significant roles in plant health, and many studies indicated that plant microbiome can suppress pathogen invasion and may reduce the outbreak of soil-borne diseases[5–7]. The use of beneficial microbiota has emerged as an alternative to chemicals in disease control and management. Plant root is the key site for the interaction between plant, microbial pathogens, and rhizosphere microbial community, and the occurrence of plant diseases is closely related to the community structure and diversity of rhizosphere microbiota[8–10]. The rhizosphere microbiota impact the

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Case Report

# Successful management of congenital bronchial web in an adolescent using bronchoscopic ablation: A case report and review of literature

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ABSTRACT

Airway webs are abnormal fibrous membranes in the airway lumen that rarely occur but can lead to serious or even life-threatening symptoms because of critical airway obstruction. Airway webs can be acquired or congenital. Acquired webs are likely to be secondary to trauma, infections, or neoplasm. Congenital laryngeal, subglottic and tracheal webs present early in infancy or childhood and are more common than congenital bronchial webs. To our knowledge, there are a few reports on the bronchial web in the literature, and the true incidence of these lesions is unknown as many probably go undetected across the lifespan.

We here report a case of a congenital bronchial web and provide a review of the literature of all reported bronchial webs. Our patient is a teenage boy who was diagnosed with a congenital bronchial web obstructing the right main-stem bronchus (RMB) and causing right lung hypoplasia and persistent right middle and right lower lobe collapse. The web was treated successfully using endoscopic ablation by argon plasma coagulation and balloon dilatation. Treatment resulted in remarkable relief of right main stem obstruction and significant improvement in right lung collapse as well as clinical, spirometric, and radiological findings.

Due to the rarity of bronchial web, the clinical knowledge and the bronchoscopic interventional strategies demonstrated of this report make it relevant. Furthermore, it emphasizes that early diagnosis and management lead to favorable clinical outcomes.

**Abbreviations**

| | |
|---|---|
| APC | Argon plasma coagulation |
| BPD | Bronchopulmonary Dysplasia |
| BW | Bronchial web |
| FB | Flexible Bronchoscopy |

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*Review*

# Resistant Chronic Spontaneous Urticaria – A Case Series Narrative Review of Treatment Options

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**Abstract**

**Background:** Chronic spontaneous urticaria (CSU) can be extremely debilitating to the patient and challenging for the treating clinician. The National Institute of Health and Clinical Excellence (NICE) in the United Kingdom (UK) recommendation of omalizumab for patients who fail to respond to high-dose anti-histamines has improved treatment options and quality of life. However, there is still lack of clear guidelines for treatment of patients resistant to standard and anti-IgE therapies.

**Methods:** We discuss the therapeutic strategies employed among nine extremely resistant CSU cases and the heterogeneity between guidelines from different societies.

**Results:** Patients with anti-histamine-resistant urticaria either remained on omalizumab or started on immunosuppressive drugs (dapsone or ciclosporin) when they stopped responding to omalizumab. We used clinical assessment, skin biopsies (when available) and previous published reports to consider dapsone (for predominantly neutrophilic infiltration), or ciclosporin at doses between 2 and 4 mg/kg/day. One patient with ciclosporin-resistant urticaria responded to mycophenolate mofetil. Two patients remain on long-term omalizumab due to its relative safety and efficacy including 1 patient with underlying antibody deficiency where omalizumab was preferred over risks of using immunosuppressive medications.

**Conclusions:** These case studies bring to light the real-world difficulties in managing patients with resistant CSU and the need for generating the evidence base on alternative therapeutic options such as synergistic use of biologics and immunosuppressive drugs.

**Keywords**

Chronic spontaneous urticaria, omalizumab, resistant urticaria, immunosuppressive drugs

## Background

Chronic spontaneous urticaria (CSU) is characterised by recurrent red, itchy cutaneous weals with central clearing, lasting for more than 6 weeks without a definite trigger. It is now well recognised that CSU forms a part of the urticarial group of disorders, which are associated with distinct skin reaction pattern with/without angioedema. Release of histamine and pro-inflammatory mediators from skin mast cells and basophils after IgE binds to its high-affinity receptor (FcεRIα) is considered the principal mechanism in CSU, but understanding the roles of autoantibodies, coagulation proteins (D-dimer) or the presence of distinct cell populations (such as eosinophils or monocytes or Th2 lymphocytes or neutrophils) on skin biopsies may provide clues into resistant CSU.[1]

A detailed clinical history and physical examination remains the cornerstone in the diagnosis of urticaria, together with a few supportive investigations that may suggest probable autoimmune or infectious aetiology. Urticaria activity

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BMC Pediatrics

CASE REPORT

Open Access

# Poland-Möbius syndrome: a case report implicating a novel mutation of the *PLXND1* gene and literature review

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## Abstract

**Background:** Möbius (Moebius) and Poland's syndromes are two rare congenital syndromes characterized by non-progressive bilateral (and often asymmetric) dysfunction of the 6th and 7th cranial nerves and hypoplasia of the pectoral muscles associated with chest wall and upper limb anomalies respectively. Manifest simultaneously as Poland-Möbius (Poland-Moebius) syndrome, debate continues as to whether this is a distinct nosological entity or represents phenotypic variation as part of a spectrum of disorders of rhomboencephalic development. Etiological hypotheses implicate both genetic and environmental factors. The *PLXND1* gene codes for a protein expressed in the fetal central nervous system and vascular endothelium and is thus involved in embryonic neurogenesis and vasculogenesis. It is located at chromosome region 3q21-q22, a locus of interest for Möbius syndrome.

**Case presentation:** We present the first report of a patient with Poland-Möbius syndrome and a mutation in the *PLXND1* gene. A child with Poland-Möbius syndrome and a maternally inherited missense variant (NM_015103.2:ex14:c.2890G > Ap.V964M) in the PLXND1 gene is described. In order to contextualize these findings, the literature was examined to identify other confirmed cases of Poland-Möbius syndrome for which genetic data were available. Fourteen additional cases of Poland-Möbius syndrome with genetic studies are described in the literature. None implicated the PLXND1 gene which has previously been implicated in isolated Möbius syndrome.

**Conclusions:** This report provides further evidence in support of a role for *PLXND1* mutations in Möbius syndrome and reasserts the nosological link between Möbius and Poland's syndromes.

**Level of evidence:** Level V, Descriptive Study.

**Keywords:** Möbius, Moebius, Poland syndrome, Symbrachydactyly, Pectoralis hypoplasia, Case report

## Background

Möbius (phonetically, Moebius) syndrome is a rare congenital disorder present in an estimated 1 per 50,000 live births and characterized by bilateral (and often asymmetric) facial paralysis with a concomitant bilateral deficit in ocular abduction. Clinically, this manifests as mask-like facies and a bilateral esotropia (convergent strabismus). Difficulties with emotional expression and social adjustment are observed in up to 40% of cases, and the debate continues regarding the extent to which this is a consequence of difficulties with non-verbal expressivity [1]. Additional manifestations may include subtle or obvious deficits in cranial nerves (especially III, IX, X and XII) [2], and cardiovascular anomalies including septal defects, vessel transposition and dextrocardia [3]. Feeding and respiratory problems also appear to be features

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nature immunology

ARTICLES

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# Congenital iRHOM2 deficiency causes ADAM17 dysfunction and environmentally directed immunodysregulatory disease

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**We report a pleiotropic disease due to loss-of-function mutations in RHBDF2, the gene encoding iRHOM2, in two kindreds with recurrent infections in different organs. One patient had recurrent pneumonia but no colon involvement, another had recurrent infectious hemorrhagic colitis but no lung involvement and the other two experienced recurrent respiratory infections. Loss of iRHOM2, a rhomboid superfamily member that regulates the ADAM17 metalloproteinase, caused defective ADAM17-dependent cleavage and release of cytokines, including tumor-necrosis factor and amphiregulin. To understand the diverse clinical phenotypes, we challenged *Rhbdf2*$^{-/-}$ mice with *Pseudomonas aeruginosa* by nasal gavage and observed more severe pneumonia, whereas infection with *Citrobacter rodentium* caused worse inflammatory colitis than in wild-type mice. The fecal microbiota in the colitis patient had characteristic oral species that can predispose to colitis. Thus, a human immunodeficiency arising from iRHOM2 deficiency causes divergent disease phenotypes that can involve the local microbial environment.**

Both genes and environment define healthy and diseased phenotypes. Many identifiable environmental factors, including geography, chemicals, infections and others, influence phenotypes associated with specific genetic variants. A classic example is phenylalanine hydroxylase deficiency[1]. Dietary intake of phenylalanine causes phenylketonuria with growth and neurological effects whereas a phenylalanine-free diet averts the neurodevelopmental phenotype but causes metabolic abnormalities[1]. Different exposures can account for the variable phenotypic expression. For the immune system, a key environmental factor is the mucosal microbiome. Conceptually, a gene defect could exhibit different organ pathology depending on the microbiome at different anatomical sites, but how this occurs in primary immunodeficiencies is unclear.

iRHOMs are rhomboid-like pseudoenzymes that facilitate trafficking, stabilization and cell surface processing of key regulatory proteins. iRHOMs contain a cytosolic N-terminal domain and an iRHOM homology domain that promote client protein interactions. One chief client of iRHOM2 is ADAM17 (tumor-necrosis factor-α

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REVIEW
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# The Human Microbiome in Chronic Kidney Disease: A Double-Edged Sword

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Chronic kidney disease (CKD) is an increasing global health burden. Current treatments for CKD include therapeutics to target factors that contribute to CKD progression, including renin–angiotensin–aldosterone system inhibitors, and drugs to control blood pressure and proteinuria control. Recently, associations between chronic disease processes and the human microbiota and its metabolites have been demonstrated. Dysbiosis—a change in the microbial diversity—has been observed in patients with CKD. The relationship between CKD and dysbiosis is bidirectional; gut-derived metabolites and toxins affect the progression of CKD, and the uremic milieu affects the microbiota. The accumulation of microbial metabolites and toxins is linked to the loss of kidney functions and increased mortality risk, yet renoprotective metabolites such as short-chain fatty acids and bile acids help restore kidney functions and increase the survival rate in CKD patients. Specific dietary interventions to alter the gut microbiome could improve clinical outcomes in patients with CKD. Low-protein and high-fiber diets increase the abundance of bacteria that produce short-chain fatty acids and anti-inflammatory bacteria. Fluctuations in the urinary microbiome are linked to increased susceptibility to infection and antibiotic resistance. In this review, we describe the potential role of the gut, urinary and blood microbiome in CKD pathophysiology and assess the feasibility of modulating the gut microbiota as a therapeutic tool for treating CKD.

**Keywords: chronic kidney disease, gut microbiota, urinary microbiome, dysbiosis, uremic toxins, renoprotective, diet therapy**

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## INTRODUCTION

Chronic kidney disease (CKD) is a growing healthcare burden affecting about 13.4% of the population worldwide (1). In the last few decades, the number of CKD patients has steadily increased (2). In adults, hypertension and diabetes are the leading causes of CKD, while congenital anomalies of the kidney and urogenital track account for the majority of CKD etiologies in children. Factors that contribute to the progression of CKD include activation of the renin–angiotensin–aldosterone system, proteinuria, a state of chronic inflammation and repetitive acute kidney injury (3–7). CKD is associated with the development of severe health conditions like cardiovascular diseases, neurological complications, adverse pregnancy outcomes, and hyperkalemia (8–12). In children, CKD affects neurocognitive abilities, school performance, growth, quality of life and the cost of medical care (6, 13–15).

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# Tipping the Balance: Vitamin D Inadequacy in Children Impacts the Major Gut Bacterial Phyla

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**Abstract:** Vitamin D inadequacy appears to be on the rise globally, and it has been linked to an increased risk of osteoporosis, as well as metabolic, cardiovascular, and autoimmune diseases. Vitamin D concentrations are partially determined by genetic factors. Specific single nucleotide polymorphisms (SNPs) in genes involved in vitamin D transport, metabolism, or binding have been found to be associated with its serum concentration, and these SNPs differ among ethnicities. Vitamin D has also been suggested to be a regulator of the gut microbiota and vitamin D deficiency as the possible cause of gut microbial dysbiosis and inflammation. This pilot study aims to fill the gap in our understanding of the prevalence, cause, and implications of vitamin D inadequacy in a pediatric population residing in Qatar. Blood and fecal samples were collected from healthy subjects aged 4–14 years. Blood was used to measure serum metabolite of vitamin D, 25-hydroxycholecalciferol 25(OH)D. To evaluate the composition of the gut microbiota, fecal samples were subjected to 16S rRNA gene sequencing. High levels of vitamin D deficiency/insufficiency were observed in our cohort with 97% of the subjects falling into the inadequate category (with serum 25(OH)D < 75 nmol/L). The CT genotype in rs12512631, an SNP in the *GC* gene, was associated with low serum levels of vitamin D (ANOVA, $p = 0.0356$) and was abundant in deficient compared to non-deficient subjects. Overall gut microbial community structure was significantly different between the deficient (D) and non-deficient (ND) groups (Bray Curtis dissimilarity $p = 0.049$), with deficient subjects also displaying reduced gut microbial diversity. Significant differences were observed among the two major gut phyla, *Firmicutes* (F) and *Bacteroidetes* (B), where deficient subjects displayed a higher B/F ratio ($p = 0.0097$) compared to ND. Vitamin D deficient children also demonstrated gut enterotypes dominated by the genus *Prevotella* as opposed to *Bacteroides*. Our findings suggest that pediatric vitamin D inadequacy significantly impacts the gut microbiota. We also highlight the importance of considering host genetics and baseline gut microbiome composition in interpreting the clinical outcomes related to vitamin D deficiency as well as designing better personalized strategies for therapeutic interventions.

**Keywords:** pediatric vitamin D deficiency; host genetics; gut microbiota; Qatar; *Bacteroidetes* to *Firmicutes* ratio

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## 1. Introduction

Vitamin D and its metabolites play a crucial role in early life, including bone growth [1] and development of the immune system [2]. Recent epidemiologic reports linking low

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CASE REPORT
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# Case Report: Phenotype-Gene Correlation in a Case of Novel Tandem 4q Microduplication With Short Stature, Speech Delay and Microcephaly

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We describe a sporadic case of a pure, tandem, interstitial chromosome 4q duplication, arr[hg19] 4q28.1q32.3 (127,008,069-165,250,477) x3 in a boy born at 36 weeks of gestation. He presented with microcephaly (head circumference <1$^{st}$ percentile), short stature (height <2$^{nd}$ percentile) and poor weight gain (weight <3$^{rd}$ percentile). Hypospadias and horseshoe shaped kidneys were also revealed following a urinary tract ultrasound. Biochemical analysis revealed normal growth hormone and thyroid hormone levels. While gross and fine motor skill development was in line with his age, speech delay was observed. This patient adds to a group of more than 30 cases of pure 4q tandem duplication with common and differing phenotypic presentations. Using a retrospective analysis of previous case studies alongside the current case and bioinformatics analysis of the duplicated region, we deduced the most likely dosage sensitive genes for some of the major phenotypes in the patient. The positive predictive value (PPV) was calculated for each gene and phenotype and was derived by comparing the previously reported patients who have gene duplications and an associated phenotype versus those who had the gene duplications but were unaffected. Thus, the growth retardation phenotype may be associated with *NAA15* duplication, speech delay with *GRIA2* and microcephaly with *PLK4* duplication. Functional studies will help in confirming the observations and elucidating the mechanisms. However, our study highlights the importance of analysing case reports with pure duplications in defining phenotype-gene relationships and in improving our knowledge of the function of precise chromosomal regions.

**Keywords: chromosomal duplication, chromosome 4, balanced translocation, rare diseases, short stature, horseshoe kidneys, speech delay, microcephaly**

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# Functional Characterization of the *MYO6* Variant p.E60Q in Non-Syndromic Hearing Loss Patients

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**Abstract:** Hereditary hearing loss (HHL) is a common genetic disorder accounting for at least 60% of pre-lingual deafness in children, of which 70% is inherited in an autosomal recessive pattern. The long tradition of consanguinity among the Qatari population has increased the prevalence of HHL, which negatively impacts the quality of life. Here, we functionally validated the pathogenicity of the c.178G>C, p.E60Q mutation in the *MYO6* gene, which was detected previously in a Qatari HHL family, using cellular and animal models. In vitro analysis was conducted in HeLa cells transiently transfected with plasmids carrying $MYO6^{WT}$ or $MYO6^{p.E60Q}$, and a zebrafish model was generated to characterize the in vivo phenotype. Cells transfected with $MYO6^{WT}$ showed higher expression of MYO6 in the plasma membrane and increased ATPase activity. Modeling the human *MYO6* variants in zebrafish resulted in severe otic defects. At 72 h post-injection, $MYO6^{p.E60Q}$ embryos demonstrated alterations in the sizes of the saccule and utricle. Additionally, zebrafish with $MYO6^{p.E60Q}$ displayed super-coiled and bent hair bundles in otic hair cells when compared to control and $MYO6^{WT}$ embryos. In conclusion, our cellular and animal models add support to the in silico prediction that the p.E60Q missense variant is pathogenic and damaging to the protein. Since the c.178G>C *MYO6* variant has a 0.5% allele frequency in the Qatari population, about 400 times higher than in other populations, it could contribute to explaining the high prevalence of hearing impairment in Qatar.

**Keywords:** sensorineural hearing loss; *MYO6*; whole-genome sequencing; zebrafish; hair cells



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## 1. Introduction

Autosomal recessive non-syndromic hearing loss (ARNSHL) accounts for more than 70% of hereditary deafness, with risk alleles traced to more than 65 loci in the human genome, including multiple sites of myosin-encoding genes [1]. Myosins are a superfamily of proteins that bind to actin and hydrolyze ATP for energy production. Myosin proteins are commonly composed of head, neck, and tail domains, which bind to actin and generate movement via the catalytic activity of the head domain. Members of the myosin superfamily follow a unified mechanoenzymatic cycle that utilizes hydrolyzed ATP for movement along actin filaments [2–4]. Briefly, the mechanoenzymatic cycle starts with the strong binding of actin to myosin to form the actomyosin complex in the absence of ATP. Once the ATP binds to myosin, this causes the dissociation of actin and the hydrolysis of ATP to ADP and inorganic phosphate (Pi). Then, actin rebinds to myosin in a weak binding state that causes a mechanical interaction. Later, the hydrolysis products ADP and Pi are released, resulting

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# Understanding the Mechanism of Diabetes Mellitus in a LRBA-Deficient Patient

**Iman Hawari [1,2,*], Johan Ericsson [1,3], Basirudeen Syed Ahamed Kabeer [2], Damien Chaussabel [2], Asma Alsulaiti [2], Sanaa A. Sharari [1,2], Cristina Maccalli [2], Faiyaz Ahmad Khan [2] and Khalid Hussain [2,*]**

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**Simple Summary:** Deficiency of lipopolysaccharide responsive beige like anchoring protein (LRBA) has been reported to cause immunological complications that can be fatal in children. Diabetes mellitus (DM) has been reported in some patients with LRBA deficiency. However, the underlying mechanism of the DM is not known. The current study provides potential novel insights into the underlying mechanism of DM in a LRBA-deficient patient. Additionally, in mouse pancreatic β-cells, we show that LRBA plays a role in the dynamics of insulin secretion and biosynthesis.

**Abstract:** The scope of this study is to show that DM in a LRBA-deficient patient with a stop codon mutation (c.3999 G > A) was not mediated through autoimmunity. We have evaluated the ability of the proband's T cells to be activated by assessing their CTLA-4 expression. A nonsignificant difference was seen in the CTLA-4 expression on CD3+ T cells compared to the healthy control at basal level and after stimulation with PMA/ionomycin. Blood transcriptomic analysis have shown a remarkable increase in abundance of transcripts related to CD71+ erythroid cells. There were no differences in the expression of modules related to autoimmunity diseases between the proband and pooled healthy controls. In addition, our novel findings show that siRNA knockdown of LRBA in mouse pancreatic β-cells leads reduced cellular proinsulin, insulin and consequently insulin secretion, without change in cell viability in cultured MIN6 cells.

**Keywords:** diabetes mellitus; autoimmunity; LRBA; CTLA-4; blood transcriptomics; insulin secretion



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## 1. Introduction

Diabtes mellitus (DM) is a complex heterogenous disease that is characterized by hyperglycemia due to insulin deficiency or resistance. DM imposes a heavy burden, and the incidence worldwide is increasing. DM seen in children can be classified according to the underlying cause of the disease, i.e., type 1 DM, type 2 DM, neonatal DM, maturity-onset diabetes of the young and syndromic forms of DM [1]. Precise and careful diagnosis of DM in infants is necessary in order to provide proper treatment and disease management [2].

Type 1A DM is characterized by immune dysregulation directed specifically against molecules associated with pancreatic insulin-producing β-cells (autoantigens), leading to insulin deficiency [3,4]. Proteins that were reported to be targeted by immune cells include: GAD65, insulinoma associated protein 2 (IA2), islet cell autoantigens (ICA1), pre-proinsulin, insulin B chain, islet-specific-glucose-6-phosphatase catalytic subunit-related protein and islet tyrosine phosphatase [5,6]. The autoimmune destruction of β-cells was shown to be mediated through infiltrating cytotoxic activity of the T lymphocytes in the pancreas [7,8].

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# A recessive variant in *SIM2* in a child with complex craniofacial anomalies and global developmental delay

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ABSTRACT

Rare deletions and duplications on the long arm of Chromosome 21 have previously been reported in many patients with craniofacial and developmental phenotypes. However, this Down Syndrome Critical Region (DSCR) contains multiple genes, making identifying a single causative gene difficult. Here, we report a case of a boy with bicoronal craniosynostosis, facial dysmorphism, developmental delay, and intellectual impairment who was found by whole genome sequencing to have a homozygous missense mutation in the Single-Minded Homolog 2 (*SIM2*) gene (c.461 A > G, p.Tyr154Cys) within the DSCR. *SIM2* encodes an essential bHLH and PAS domain transcription factor expressed during fetal brain development and acts as a master regulator of neurogenesis. This variant is globally very rare, segregates in the family, and is predicted to be highly deleterious by *in silico* analysis, 3D molecular modeling of protein structure, and functional analysis of zebrafish models. Zebrafish expressing the human SIM2$^{p.Y154C}$ variant displayed a progressed microcephaly-like phenotype and head shape abnormalities. When combined with careful phenotyping of the patient vis-à-vis previously reported cases harboring structural variants in this critical 21q22 region, the data support a pathogenic role of *SIM2* in this complex syndrome and demonstrates the utility of next-generation sequencing in prioritizing genes in contiguous deletions/duplications syndromes and diagnosing microarray-negative patients in the craniofacial clinic.

## 1. Introduction

Human single-minded 2 homolog gene (*SIM2*) encodes a 667 amino acid protein that is part of a family of basic helix-loop-helix (bHLH) and the PER-ARNT-SIM (PAS) domains transcription factors that play an essential role in central nervous system midline cell development and gene expression (Nambu et al., 1990, 1991). Human *SIM2* was initially identified by exon trapping from a Down syndrome critical region (DSCR) on chromosome 21 and was suggested to be a candidate gene for association with many of the pathophysiological features of Down syndrome, including brain development abnormalities, facial dysmorphology, and intellectual impairment, primarily due to its expression at fetal stages of brain development and within regions outside the brain consistent with sites of Down syndrome clinical hallmarks (Rahmani et al., 1989; Chen et al., 1995; Yamaki et al., 1996; Rachidi et al., 2005). However, to date no patients harboring *SIM2* point-mutations had been reported, and thus the evidence for causality had been largely due to its location within the DSCR, in which contiguous gene deletions or duplications overlapping SIM2 (up to 70 genes in some reports) cause craniofacial anomalies and various developmental disorders. Further, mouse *Sim2* – mapping to mouse chromosome 16 and syntenic to the chromosome 21 DSCR in humans – is mainly expressed in the brain, craniofacial structure, and muscles (Fan et al., 1996; Yamaki et al., 2001), and complete knockout of *Sim2* leads to lethality with notable craniofacial anomalies, further highlighting its role in normal craniofacial development (Shamblott et al., 2002).

Here, we report the first homozygous protein-altering mutation in *SIM2* in a 7-year-old boy presenting with multiple craniofacial and eye anomalies, developmental delay and intellectual impairment. Further, by comparing clinical features across case series harboring structural

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# The Impact of Nutritional Supplementation During Pregnancy on the Incidence of Gestational Diabetes and Glycaemia Control

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The nutritional state before and throughout pregnancy has a critical impact on the women's health and the baby's development and growth. The release of placental hormones during pregnancy induces/ increases maternal insulin resistance and promotes nutrition utilization by the fetus. Gestational Diabetes Mellitus (GDM) is the most common medical complication in pregnancy and is associated with significant maternal and fetal morbidity. Several studies have examined the effect of physical activity, healthy eating, and various food supplements on the risk of developing gestational diabetes (GDM) and related outcomes. Among those, Myo-Inositol supplementation has shown encouraging results in the prevention of GDM. Maternal vitamin D deficiency has been associated with an elevated risk of GDM, and supplementation can improve glucose haemostasis by lowering fasting blood glucose, HbA1c, and serum insulin concentration. Probiotics modulate the gut microbiota leading to an improved glucose and lipid metabolism, which is proposed to reduce the risk of GDM. We aim to review the strength and limitation of the current evidence for using some nutritional supplements either as single agents or in combinations on the risk of developing GDM and on glycaemic control.

**Keywords: pregnancy, gestational diabetes, Myo-Inositol, probiotics, vitamin D, fish oils, omega 3**

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## INTRODUCTION

Appropriate nutritional health before and during pregnancy is essential for favorable outcomes and the long-term health of the offspring. One or more nutritional deficits in mothers before and in early pregnancy are not uncommon and increase adverse pregnancy outcomes. Gestational diabetes mellitus (GDM) is a common pregnancy disorder associated with an increased risk of pregnancy complications and long-term metabolic complications for both mothers and offspring (1). Pre-eclamptic toxemia, preterm labor, large for gestational age, neonatal hypoglycaemia, and cesarean delivery are serious pregnancy complications associated with GDM. Besides, GDM increases the future risk of hypertension, type 2 diabetes (T2DM), fatty liver disease, and cardiovascular disease in women and offspring (1).

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# Gut microbial influences on the adaptive immune system and the development of cow milk allergy

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## ABSTRACT

Allergic diseases constitute significant health and economic issues in both developed and developing nations, with epidemiological studies demonstrating a rapid increase in the global prevalence of food allergy among the pediatric population. Cow milk protein allergy (CMPA), one of the most common forms of food allergies observed in early childhood, affects between 2% – 6% of infants and children under 3 years of age. CMPA can present as either an IgE-mediated atopic allergy or a non-IgE mediated allergic response. Antigen-specific T cells play a pivotal role in directing the type of inflammatory immune response that occurs as well as in the formation of immunological memory. IgE-mediated CMPA is thought to develop because of an abnormal expansion of allergen-specific type-2 helper T (Th2) cells and a corresponding deficiency in immune regulation by regulatory T cells (Tregs), thereby altering the Th2/Treg balance. The gut microbiota, established very early during childhood through host-microbe interactions, can influence the incidence of allergic diseases. In this study, we aimed to analyze both the microbiome composition and CD4 + T cell differentiation patterns in pediatric patients with and without cow milk allergy to establish the association between these factors. Using 16S rRNA sequencing, we analyzed the microbiome composition in stool samples of allergic and non-allergic pediatric patients aged between 1 – 4 years and identified the microbial species abundant in IgE and non-IgE mediated cow milk allergies. To assess the CD4 + T cell differentiation patterns, peripheral blood mononuclear cells (PBMCs) from these patients were re-stimulated with cow milk antigen, and T cell subsets were assessed

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ORIGINAL RESEARCH
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# Understanding the Mechanism of Dysglycemia in a Fanconi-Bickel Syndrome Patient

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Fanconi–Bickel Syndrome (FBS) is a rare disorder of carbohydrate metabolism that is characterized mainly by the accumulation of glycogen in the liver and kidney. It is inherited as an autosomal recessive disorder caused by mutations in the *SLC2A2* gene, which encodes for GLUT2. Patients with FBS have dysglycemia but the molecular mechanisms of dysglycemia are still not clearly understood. Therefore, we aimed to understand the underlying molecular mechanisms of dysglycemia in a patient with FBS. Genomic DNA was isolated from a peripheral blood sample and analyzed by whole genome and Sanger sequencing. CRISPR-Cas9 was used to introduce a mutation that mimics the patient's mutation in a human kidney cell line expressing GLUT2 (HEK293T). Mutant cells were used for molecular analysis to investigate the effects of the mutation on the expression and function of GLUT2, as well as the expression of other genes implicated in dysglycemia. The patient was found to have a homozygous nonsense mutation (c.901C>T, R301X) in the *SLC2A2* gene. CRISPR-Cas9 successfully mimicked the patient's mutation in HEK293T cells. The mutant cells showed overexpression of a dysfunctional GLUT2 protein, resulting in reduced glucose release activity and enhanced intracellular glucose accumulation. In addition, other glucose transporters (SGLT1 and SGLT2 in the kidney) were found to be induced in the mutant cells. These findings suggest the last loops (loops 9-12) of GLUT2 are essential for glucose transport activity and indicate that GLUT2 dysfunction is associated with dysglycemia in FBS.

**Keywords: Fanconi-Bickel syndrome (FBS), dysglycemia, glucose transporter 2 (GLUT2), clustered regularly interspaced short palindromic repeats (CRISPR)- Cas9, sodium-glucose transport protein 2 (SGLT2)**

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## INTRODUCTION

The classical phenotype of Fanconi-Bickel Syndrome (FBS) was initially described by 1 (1). GLUT2 mutations were first described in three FBS patients, including the original patient in 1997 (2). More than 100 FBS cases with different *SLC2A2* mutations; nonsense, missense, Fs/InDel, intronic, and compound heterozygous variants have been reported so far (3–8). *SLC2A2* gene consists of 11 exons

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RESEARCH Open Access

# The immune landscape of solid pediatric tumors

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## Abstract

**Background:** Large immunogenomic analyses have demonstrated the prognostic role of the functional orientation of the tumor microenvironment in adult solid tumors, this variable has been poorly explored in the pediatric counterpart.

**Methods:** We performed a systematic analysis of public RNAseq data (TARGET) for five pediatric tumor types (408 patients): Wilms tumor (WLM), neuroblastoma (NBL), osteosarcoma (OS), clear cell sarcoma of the kidney (CCSK) and rhabdoid tumor of the kidney (RT). We assessed the performance of the Immunologic Constant of Rejection (ICR), which captures an active Th1/cytotoxic response. We also performed gene set enrichment analysis (ssGSEA) and clustered more than 100 well characterized immune traits to define immune subtypes and compared their outcome.

**Results:** A higher ICR score was associated with better survival in OS and high risk NBL without MYCN amplification but with poorer survival in WLM. Clustering of immune traits revealed the same five principal modules previously described in adult tumors (TCGA). These modules divided pediatric patients into six immune subtypes (S1-S6) with distinct survival outcomes. The S2 cluster showed the best overall survival, characterized by low enrichment of the wound healing signature, high Th1, and low Th2 infiltration, while the reverse was observed in S4. Upregulation of the WNT/Beta-catenin pathway was associated with unfavorable outcomes and decreased T-cell infiltration in OS.

**Conclusions:** We demonstrated that extracranial pediatric tumors could be classified according to their immune disposition, unveiling similarities with adults' tumors. Immunological parameters might be explored to refine diagnostic and prognostic biomarkers and to identify potential immune-responsive tumors.

**Keywords:** Pediatric cancer, Neuroblastoma, Osteosarcoma, Immune phenotypes

## Background

Cancer is one of the leading causes of death in children worldwide, and the recorded incidence tends to rise with time [1]. In the US [2], and in other high-income countries [3], cancer is the leading cause of death by disease past infancy among children.

The overall incidence rates of childhood cancer vary between 50 and 200 per million children across the world [1]. The most common categories of childhood cancers include leukemias, brain tumors, lymphomas, neuroblastoma and nephroblastoma (Wilms tumor, WLM) [4]. Solid tumors comprise almost half of the cancer cases [5]. Neuroblastoma (the most frequent pediatric extra-cranial tumor) and WLM are tumor types that occur almost exclusively in children [6].

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Molecular Case Studies

RESEARCH REPORT

# A de novo start-loss in *EFTUD2* associated with mandibulofacial dysostosis with microcephaly: case report

Muhammad Kohailan,[1] Omayma Al-Saei,[2] Sujitha Padmajeya,[2] Waleed Aamer,[2] Najwa Elbashir,[2] Ammira Al-Shabeeb Akil,[2] Abdul-Rauf Kamboh,[3] and Khalid Fakhro[1,2,4]

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**Abstract** Mandibulofacial dysostosis with microcephaly (MFDM) is a rare genetic disorder inherited in an autosomal dominant pattern. Major characteristics include developmental delay, craniofacial malformations such as malar and mandibular hypoplasia, and ear anomalies. Here, we report a 4.5-yr-old female patient with symptoms fitting MFDM. Using whole-genome sequencing, we identified a de novo start-codon loss (c.3G > T) in the *EFTUD2*. We examined *EFTUD2* expression in the patient by RNA sequencing and observed a notable functional consequence of the variant on gene expression in the patient. We identified a novel variant for the development of MFDM in humans. To the best of our knowledge, this is the first report of a start-codon loss in *EFTUD2* associated with MFDM.

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**Ontology terms:**
mandibulofacial dysostosis; microcephaly

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## INTRODUCTION

Mandibulofacial dysostosis with microcephaly (MFDM; also known as Guion-Almeida type; MIM #610536) is a rare autosomal dominant disorder characterized by developmental delay and several craniofacial malformations, including micrognathia, malar hypoplasia, ear anomalies, microcephaly, cleft palate, and facial asymmetry. In some cases, involvement of other organs have been reported, such as thumb anomalies, heart defects, esophageal atresia, and renal malformations (Guion-Almeida et al. 2006; Wieczorek et al. 2007; Guion-Almeida et al. 2009; Wieczorek et al. 2009). Patients may also present with eye abnormalities, including microphthalmia, microcornea, coloboma, and myopia (Deml et al. 2015).

From a total of 119 previously reported MFDM patients in the literature (Huang et al. 2016; Matsuo et al. 2017; Rengasamy Venugopalan et al. 2017; Yu et al. 2018; Lacour et al. 2019; Silva et al. 2019; Jacob et al. 2020; Kim et al. 2020; Narumi-Kishimoto et al. 2020; Xu et al. 2021a; Li et al. 2022), 95 cases (80%) were found to harbor deleterious variants in *Elongation Factor Tu GTP Binding Domain Containing 2* gene (*EFTUD2*; MIM #603892). In 76 cases both parents were also genotyped, and 60 (79%) were found to have de novo variants. The remaining were either germline mosaic or inherited in an autosomal dominant manner (Huang et al. 2016). The human *EFTUD2* encodes the U5-116kD nuclear protein, which plays a critical role in the pre-mRNA splicing process (Fabrizio et al. 1997). Recent

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*Review*

# Inflammatory Bowel Disease Treatments and Predictive Biomarkers of Therapeutic Response

**Duaa Ahmed Elhag [1,†], Manoj Kumar [1,†], Marwa Saadaoui [1], Anthony K. Akobeng [2], Fatma Al-Mudahka [2], Mamoun Elawad [2] and Souhaila Al Khodor [1,*]**

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**Abstract:** Inflammatory bowel disease (IBD) is a chronic immune-mediated inflammation of the gastrointestinal tract with a highly heterogeneous presentation. It has a relapsing and remitting clinical course that necessitates lifelong monitoring and treatment. Although the availability of a variety of effective therapeutic options including immunomodulators and biologics (such as TNF, CAM inhibitors) has led to a paradigm shift in the treatment outcomes and clinical management of IBD patients, some patients still either fail to respond or lose their responsiveness to therapy over time. Therefore, according to the recent Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) recommendations, continuous disease monitoring from symptomatic relief to endoscopic healing along with short- and long-term therapeutic responses are critical for providing IBD patients with a tailored therapy algorithm. Moreover, considering the high unmet need for novel therapeutic approaches for IBD patients, various new modulators of cytokine signaling events (for example, JAK/TYK inhibitors), inhibitors of cytokines (for example IL-12/IL-23, IL-22, IL-36, and IL-6 inhibitors), anti-adhesion and migration strategies (for example, β7 integrin, sphingosine 1-phosphate receptors, and stem cells), as well as microbial-based therapeutics to decolonize the bed buds (for example, fecal microbiota transplantation and bacterial inhibitors) are currently being evaluated in different phases of controlled clinical trials. This review aims to offer a comprehensive overview of available treatment options and emerging therapeutic approaches for IBD patients. Furthermore, predictive biomarkers for monitoring the therapeutic response to different IBD therapies are also discussed.

**Keywords:** IBD; precision medicine; Crohn's disease; ulcerative colitis; biomarkers; biological treatment



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## 1. Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing inflammatory disorder of the gastrointestinal (GI) tract [1]. Multiple factors including urbanization, westernization, dietary changes, increased antimicrobial exposure, and other factors affecting host–microbial homeostasis have been linked to an increase in the prevalence of IBD [2]. IBD is a chronic disease that causes progressive structural and functional damage to the GI tract and intestinal epithelium [3] requiring lifelong medication [1]. IBD is classified into two major subtypes based on pathological features and disease manifestation: Ulcerative Colitis (UC), which primarily affects the colon, and Crohn's disease (CD), which affects multiple GI sites, suggesting that these subtypes are distinct clinical entities that require distinct clinical management [4,5]. CD and UC are considered highly heterogeneous and complex, which further complicates the clinical management and treatment plans for those patients [5].

A better understanding of disease biology and heterogeneity has resulted in the development of broad-spectrum and disease-specific molecules employed for precise targeting,

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# Female infertility and diet, is there a role for a personalized nutritional approach in assisted reproductive technologies? A Narrative Review

Amira Kohil[1†], Spyridon Chouliaras[2†], Shaikha Alabduljabbar[1], Arun Prasath Lakshmanan[1], Salma Hayder Ahmed[1], Johnny Awwad[2] and Annalisa Terranegra[1*]

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Female infertility is a major public health concern and a global challenge. It is a disorder of the reproductive system, defined as the inability to achieve a clinical pregnancy. Nutrition and other environmental factors are found to impact reproductive health in women as well as the outcome of assisted reproductive technologies (ART). Dietary factors, such as polyunsaturated fatty acids (PUFA), fiber as well as the intake of Mediterranean diet appear to exert beneficial effects on female reproductive outcomes. The exact mechanisms associating diet to female fertility are yet to be identified, although genomic, epigenomic, and microbial pathways may be implicated. This review aims to summarize the current knowledge on the impact of dietary components on female reproduction and ART outcomes, and to discuss the relevant interplay of diet with genome, epigenome and microbial composition.

KEYWORDS

**diet, fertility, female reproductive health, art, nutrigenetics, nutrigenomics, nutriepigenome, microbiome**

## Introduction

According to the WHO, infertility is a global health issue affecting around 48 million couples around the world (1). Infertility is a disorder of the reproductive system defined as the inability to develop clinical pregnancy after 1 year of unprotected sexual intercourse (1). It is estimated that up to 15% of reproductive-aged couples worldwide are affected (1). Despite recent scientific advances and increased access and use of Assisted Reproductive Technologies (ART) globally, the overall burden of infertility has not shown any decline over the last two decades. Indeed, although *in vitro* fertilization (IVF) has revolutionized the landscape of infertility treatment, it remains far from being a panacea and success rates over the recent years have plateaued (2). The increasing prevalence of female impaired

genes

MDPI

*Article*

# Investigation of Genetic Causes in Patients with Congenital Heart Disease in Qatar: Findings from the Sidra Cardiac Registry

**Sarah Okashah [1], Dhanya Vasudeva [2], Aya El Jerbi [3], Houssein Khodjet-El-khil [1], Mashael Al-Shafai [1], Najeeb Syed [2], Marios Kambouris [4], Sharda Udassi [5,6], Luis R. Saraiva [2,7,8], Hesham Al-Saloos [3], Jai Udassi [3,9] and Kholoud N. Al-Shafai [2,*]**

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**Abstract:** Congenital heart disease (CHD) is one of the most common forms of birth defects worldwide, with a prevalence of 1–2% in newborns. CHD is a multifactorial disease partially caused by genetic defects, including chromosomal abnormalities and single gene mutations. Here, we describe the Sidra Cardiac Registry, which includes 52 families and a total of 178 individuals, and investigate the genetic etiology of CHD in Qatar. We reviewed the results of genetic tests conducted in patients as part of their clinical evaluation, including chromosomal testing. We also performed whole exome sequencing (WES) to identify potential causative variants. Sixteen patients with CHD had chromosomal abnormalities that explained their complex CHD phenotype, including six patients with trisomy 21. Moreover, using exome analysis, we identified potential CHD variants in 24 patients, revealing 65 potential variants in 56 genes. Four variants were classified as pathogenic/likely pathogenic based on the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) classification; these variants were detected in four patients. This study sheds light on several potential genetic variants contributing to the development of CHD. Additional functional studies are needed to better understand the role of the identified variants in the pathogenesis of CHD.

**Keywords:** congenital heart defect; Qatar; genetic investigation; whole exome sequencing; single-nucleotide variant; chromosomal abnormalities

## 1. Introduction

Congenital heart disease (CHD) is one of the most common birth defects worldwide, with a general prevalence of 1–2% in newborns [1]. The prevalence of specific manifestations of CHD varies significantly in different populations, and their genetic etiology is incredibly complex [2]. For example, sporadic cases account for 5–10% of all cases of CHD with a

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BioData Mining

RESEARCH Open Access

# Analysis of risk factors progression of preterm delivery using electronic health records

Zeineb Safi[1†], Neethu Venugopal[1], Haytham Ali[2], Michel Makhlouf[3], Faisal Farooq[4] and Sabri Boughorbel[4*†]

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## Abstract

**Background:** Preterm deliveries have many negative health implications on both mother and child. Identifying the population level factors that increase the risk of preterm deliveries is an important step in the direction of mitigating the impact and reducing the frequency of occurrence of preterm deliveries. The purpose of this work is to identify preterm delivery risk factors and their progression throughout the pregnancy from a large collection of Electronic Health Records (EHR).

**Results:** The study cohort includes about 60,000 deliveries in the USA with the complete medical history from EHR for diagnoses, medications and procedures. We propose a temporal analysis of risk factors by estimating and comparing risk ratios and variable importance at different time points prior to the delivery event. We selected the following time points before delivery: 0, 12 and 24 week(s) of gestation. We did so by conducting a retrospective cohort study of patient history for a selected set of mothers who delivered preterm and a control group of mothers that delivered full-term. We analyzed the extracted data using logistic regression and random forests models. The results of our analyses showed that the highest risk ratio and variable importance corresponds to history of previous preterm delivery. Other risk factors were identified, some of which are consistent with those that are reported in the literature, others need further investigation.

**Conclusions:** The comparative analysis of the risk factors at different time points showed that risk factors in the early pregnancy related to patient history and chronic condition, while the risk factors in late pregnancy are specific to the current pregnancy. Our analysis unifies several previously reported studies on preterm risk factors. It also gives important insights on the changes of risk factors in the course of pregnancy. The code used for data analysis will be made available on github.

**Keywords:** Preterm, Pregnancy, EHR, Epidemiology, Risk factors, Progression, Temporal analysis, Precision medicine, Predictive models

biomedicines

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*Article*

# Understanding the Role of GLUT2 in Dysglycemia Associated with Fanconi–Bickel Syndrome

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**Abstract:** Fanconi–Bickel Syndrome (FBS) is a rare disorder of carbohydrate metabolism that is characterized by the accumulation of glycogen mainly in the liver. It is inherited in an autosomal recessive manner due to mutations in the *SLC2A2* gene. *SLC2A2* encodes for the glucose transporter GLUT2 and is expressed in tissues that are involved in glucose homeostasis. The molecular mechanisms of dysglycemia in FBS are still not clearly understood. In this study, we report two cases of FBS with classical phenotypes of FBS associated with dysglycemia. Genomic DNA was extracted and analyzed by whole-genome and Sanger sequencing, and patient PBMCs were used for molecular analysis. One patient had an exonic *SLC2A2* mutation (c.1093C>T in exon 9, R365X), while the other patient had a novel intronic *SLC2A2* mutation (c.613-7T>G). Surprisingly, the exonic mutation resulted in the overexpression of dysfunctional GLUT2, resulting in the dysregulated expression of other glucose transporters. The intronic mutation did not affect the coding sequence of GLUT2, its expression, or glucose transport activity. However, it was associated with the expression of miRNAs correlated with type 1 diabetes mellitus, with a particular significant overexpression of hsa-miR-29a-3p implicated in insulin production and secretion. Our findings suggest that *SLC2A2* mutations cause dysglycemia in FBS either by a direct effect on GLUT2 expression and/or activity or, indirectly, by the dysregulated expression of miRNAs implicated in glucose homeostasis.

**Keywords:** Fanconi–Bickel syndrome (FBS); dysglycemia; glucose transporter 2 (GLUT2); PBMCs (peripheral blood mononuclear cells); miRNAs

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## 1. Introduction

Fanconi and Bickel initially reported the clinical features of the eponymous syndrome (FBS) in 1949 [1]. Mutations in glucose transporter 2 (GLUT2) were first reported in three FBS patients, including the first patient in 1997 [2]. More than 100 FBS cases with different *SLC2A2* mutations (missense, nonsense, Fs/InDel, intronic, and compound heterozygous) have been reported to date [3–9]. The *SLC2A2* gene encodes for low-affinity-facilitated glucose transporter 2 (GLUT2, SLC2A2-201 ENST00000314251.8) [3,10]. GLUT2 is expressed in tissues that play a vital role in glucose homeostasis; GLUT2 in the intestine absorbs glucose from the diet and transports it to the blood [11,12].

GLUT2 in the human liver is considered to be a bidirectional transporter. It is involved in taking up glucose for storage as glycogen during the feeding state. It also plays a role in releasing glucose generated either by gluconeogenesis or glycogenolysis during fasting [13–15]. Fasting hypoglycemia, postprandial hyperglycemia, and glycogen storage in FBS patients can be explained by a disturbance in glucose transport and metabolism in the liver. In addition, in the kidney, GLUT2 releases the reabsorbed glucose back to the

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# Characterization of the Urinary Metagenome and Virome in Healthy Children

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**Abstract:** Recent advances in next-generation sequencing and metagenomic studies have provided insights into the microbial profile of different body sites. However, research on the microbial composition of urine is limited, particularly in children. The goal of this study was to optimize and develop reproducible metagenome and virome protocols using a small volume of urine samples collected from healthy children. We collected midstream urine specimens from 40 healthy children. Using the metagenomics shotgun approach, we tested various protocols. Different microbial roots such as Archaea, Bacteria, Eukaryota, and Viruses were successfully identified using our optimized urine protocol. Our data reflected much variation in the microbial fingerprints of children. Girls had significantly higher levels of Firmicutes, whereas boys had significantly higher levels of Actinobacteria. The genus *Anaerococcus* dominated the urinary bacteriome of healthy girls, with a significant increase in *Anaerococcus prevotii*, *Anaerococcus vaginalis*, and *Veillonella parvula* ($p$-value < 0.001) when compared with that of boys. An increased relative abundance of *Xylanimonas* and *Arthrobacter*, with a significantly high abundance of *Arthrobacter* sp. *FB24* ($p$-value 0.0028) and *Arthrobacter aurescences* ($p$-value 0.015), was observed in boys. The urinary mycobiome showed a significant rise in the genus *Malassezia* and *Malassezia globose* fungus ($p$-value 0.009) in girls, whereas genus *Saccharomyces* ($p$-value 0.009) was significantly high in boys. The beta diversity of the urinary mycobiome was found to differ between different age groups. Boys had significantly more *Mastadenovirus* and *Human mastadenovirus-A* in their urinary virome than girls. With increasing age, we noticed an increase in the relative abundance of the order Caudovirales. Our optimized protocols allowed us to identify the unique microbes for each sex by using an adequate volume of urine (3–10 mL) to screen for the bacteriome, mycobiome, and virome profiles in the urine of healthy children. To the best of our knowledge, this is the first study to characterize the metagenomics profiles of urine in a healthy pediatric population.

**Keywords:** urine metagenome; urine mycobiome; urine virome; healthy children; pediatric population



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## 1. Introduction

The human microbiome is composed of all of the genes of the bacteria, fungi, viruses, archaea, and other types of microbes living inside or on our body [1]. The majority of the human microbiome is located in the gut [2]. The number of gut microbiota is estimated to be more than $10^{14}$, and the genomic content of the microbiota is 100 times more than that of the human genome [3]. Due to the large populations of bacteria present at this site and the ease with which feces can be obtained as a representative sample for the gut microbiota, the gut microbiome has been extensively studied [4].

In the past, urine was considered a sterile fluid that only became unsterile after infection [5–7]. As a result, urine microorganisms were only detected in clinical microbiology

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RESEARCH

# Effects of inhaled nitric oxide (iNO) in pulmonary hypertension secondary to arteriovenous malformations: a retrospective cohort study from the European iNO registry

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## Abstract

This study aims to assess the effects of inhaled nitric oxide (iNO) on oxygenation in the management of pulmonary hypertension (PH) secondary to arteriovenous malformations (AVMs) in neonates. This is a matched retrospective cohort study from January 1, 2013, to December 31, 2017. The European inhaled nitric oxide registry from 43 neonatal and pediatric ICUs in 13 countries across Europe was used to extract data. The target population was neonates treated with iNO for the management of PH. The cases (PH secondary to AVMs treated with iNO) were matched (1:4 ratio) to controls (PH without AVMs treated with iNO). The main outcome measure was the absolute change of oxygenation index (OI) from baseline to 60 min after starting iNO in cases and controls. The primary outcome of our study was that the mean absolute change in OI from baseline to after 60 min was higher among cases 10.7 (14), than in controls 6 (22.5), and was not statistically different between the groups. The secondary outcome variable — death before discharge — was found to be significantly higher in cases (55%) than in controls (8%). All the other variables for secondary outcome measures remained statistically insignificant.

*Conclusion*: Infants with PH secondary to AVMs treated with iNO did not respond differently compared to those presented with PH without AVMs treated with iNO. Right ventricular dysfunction on echocardiography was higher in cases than controls (cases: 66.7% and controls: 28.6%) but was not statistically significant.

**What is Known:**

- *Arterioenous malformation (AVM) is a well-known cause of persistent pulmonary hypertension in newborns. Inhaled nitric oxide (iNO) is most commonly used as first-line therapy for pulmonary hypertension in newborns.*
- *Around 40–50% of vein of Galen malformations (VOGMs) are found to have congestive heart failure in the neonatal period.*

**What is New:**

- *Neonates may present with an isolated PH of the newborn as the main feature of the VOGMs. A large proportion of cases with AVMs have been associated with right ventricular cardiac dysfunction.*
- *Results from one of the largest database registries in the world for iNO have been used to answer our research question.*

**Keywords** Nitric oxide · Pulmonary hypertension · Arteriovenous malformations · Oxygenation index · Hemodynamics · Neonates

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ARTICLE

# Impaired IL-23–dependent induction of IFN-γ underlies mycobacterial disease in patients with inherited TYK2 deficiency

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Bernhard Fleckenstein died on May 4, 2021. *M. Ogishi, A.A. Arias, R. Yang, and J.E. Han are joint first authors, with equal contributions; **Z. Pourmoghaddas, S. Bakhtiar, A.M. Willasch, G. Horneff, G. Llanora, L.P. Shek, L.Y.A. Chai, S.H. Tay, H.H. Rahimi, S.A. Mahdaviani, S. Nepesov, A.A. Bousfiha, E.H. Erdeniz, A. Karbuz, N. Marr, C. Navarette, M. Adeli, L. Hammarstrom, H. Abolhassani, N. Parvaneh, S. Al Muhsen, M.F. Alosaimi, F. Alsohime, M. Nourizadeh, M. Moin, R. Arnaout, S. Alshareef, J. El-Baghdadi, F. Genel, R. Sherkat, A. Kiykim, E. Yücel, and S. Keles contributed equally to this paper; ***J. Bustamante and L. Abel are joint penultimate authors, with equal contributions; ****J.-L. Casanova and S. Boisson-Dupuis are joint last authors, responsible for joint supervision of the study. Correspondence to Jean-Laurent Casanova: casanova@rockefeller.edu; Stéphanie Boisson-Dupuis: stbo603@rockefeller.edu

**Human cells homozygous for rare loss-of-expression (LOE) *TYK2* alleles have impaired, but not abolished, cellular responses to IFN-α/β (underlying viral diseases in the patients) and to IL-12 and IL-23 (underlying mycobacterial diseases). Cells homozygous for the common P1104A *TYK2* allele have selectively impaired responses to IL-23 (underlying isolated mycobacterial disease). We report three new forms of TYK2 deficiency in six patients from five families homozygous for rare *TYK2* alleles (R864C, G996R, G634E, or G1010D) or compound heterozygous for P1104A and a rare allele (A928V). All these missense alleles encode detectable proteins. The R864C and G1010D alleles are hypomorphic and loss-of-function (LOF), respectively, across signaling pathways. By contrast, hypomorphic G996R, G634E, and A928V mutations selectively impair responses to IL-23, like P1104A. Impairment of the IL-23–dependent induction of IFN-γ is the only mechanism of mycobacterial disease common to patients with complete TYK2 deficiency with or without TYK2 expression, partial TYK2 deficiency across signaling pathways, or rare or common partial TYK2 deficiency specific for IL-23 signaling.**

## Introduction

Mendelian susceptibility to mycobacterial disease (MSMD) is characterized by severe diseases caused by weakly virulent mycobacteria, such as bacillus Calmette-Guérin (BCG) vaccines and environmental mycobacteria (EM) in otherwise healthy patients, normally resistant to other microorganisms and without overt immunodeficiency (Casanova and Abel, 2002, 2018, 2022; Bustamante et al., 2014; Bustamante, 2020; Boisson-Dupuis and Bustamante, 2021). Patients with "isolated MSMD" have the canonical MSMD phenotype, whereas patients with "syndromic MSMD" also typically display other clinical phenotypes, infectious or otherwise. Germline mutations of 19 genes underlie 34 forms of MSMD due to allelic heterogeneity (Bustamante, 2020; Kerner et al., 2020; Le Voyer et al., 2021; Martin-Fernandez et al., 2022; Yang et al., 2020). Most known genetic etiologies of MSMD affect the production of or cellular response to IFN-γ, highlighting the indispensable role of this cytokine in the control of mycobacteria (Boisson-Dupuis and Bustamante, 2021; Boisson-Dupuis et al., 2018; Bustamante, 2020; Kerner et al., 2020; Le Voyer et al., 2021; Martinez-Barricarte et al., 2018; Yang et al., 2020). One possible exception is ZNFX1 deficiency, for which the pathogenic mechanism remains unknown (Le Voyer et al., 2021). Human IFN-γ has been shown to function more as a macrophage-activating factor than as an antiviral interferon (Nathan et al., 1983). The susceptibility of IFN-γ–deficient mice to weakly virulent mycobacteria is consistent with these findings (Dalton et al., 1993; Doherty and Sher, 1997; Kamijo et al., 1993). Inborn errors of IFN-γ immunity can also underlie infections caused by *Mycobacterium tuberculosis* (*M.tb*), which is ≥1,000 times more virulent than BCG (Boisson-Dupuis, 2020; Boisson-Dupuis and Bustamante, 2021; Ogishi et al., 2021; Casanova and Abel, 2022), and a few other intramacrophagic pathogens, including bacteria (e.g., *Salmonella*), parasites (e.g., *Leishmania*), and fungi (e.g., *Histoplasma*; Arias et al., 2017; Bustamante, 2020; Bustamante et al., 2014; de Beaucoudrey et al., 2010; Parvaneh et al., 2017; Tan et al., 2016; van de Vosse et al., 2013). Patients with syndromic MSMD display associated phenotypes: patients with ISG15 deficiency have features of type I interferonopathy (Bogunovic et al., 2012; Martin-Fernandez et al., 2020; Zhang et al., 2015), patients with RORγ/RORγT deficiency have chronic mucocutaneous candidiasis (Okada et al., 2015), patients with ZNFX1 deficiency have monocytosis (Le Voyer et al., 2021), the only patient with T-bet deficiency reported to date has airway hyperresponsiveness (Yang et al., 2021), and patients with JAK1 or TYK2 deficiencies have viral diseases (Eletto et al., 2016; Kreins et al., 2015).

Autosomal recessive (AR) complete TYK2 deficiency is characterized by mycobacterial and/or viral diseases (Table 1; Fuchs et al., 2016; Guo et al., 2020; Kreins et al., 2015; Minegishi et al., 2006; Sarrafzadeh et al., 2020; Wu et al., 2020; Zhang et al., 2022). Only 15 patients with AR TYK2 deficiency from 13 families have been reported (including one for whom functional characterization is incomplete; Table 1; Fuchs et al., 2016; Guo et al., 2020; Kilic et al., 2012; Kreins et al., 2015; Minegishi et al., 2006; Sarrafzadeh et al., 2020; Wu et al., 2020; Zhang et al., 2022). Nine of these patients had mycobacterial diseases, including BCG disease ($n$ = 6), EM disease ($n$ = 1), and tuberculosis (TB; $n$ = 3), and five had unusually severe viral illnesses, including mucocutaneous herpes simplex virus 1 (HSV-1) infections ($n$ = 3), HSV-1 encephalitis (HSE; $n$ = 1), cutaneous varicella-zoster virus (VZV; $n$ = 2) or *Molluscum contagiosum* ($n$ = 1) infections, human parainfluenza type 3 virus (PIV3) pneumonia ($n$ = 1), COVID-19 pneumonia ($n$ = 4), influenza A pneumonia ($n$ = 1), and measles-mumps-rubella (MMR) vaccine disease ($n$ = 1; Fuchs et al., 2016; Guo et al., 2020; Kilic et al., 2012; Kreins et al., 2015; Minegishi et al., 2006; Sarrafzadeh et al., 2020; Wu et al., 2020; Zhang et al., 2022). AR TYK2 deficiency impairs, but does not abolish, cellular responses to IL-10, IL-12, IL-23, and IFN-α/β (Kreins et al., 2015; Minegishi et al., 2006). Poor responses to IFN-α/β in most if not all cell types underlie viral diseases, whereas poor IFN-γ induction in lymphocytes stimulated with IL-12 or IL-23 underlies mycobacterial diseases. Patient P-Jap (Minegishi et al., 2006) was the only TYK2-deficient patient reported to suffer from chronic mucocutaneous candidiasis, which was attributed to impaired IL-12 and IL-23 responses and defective Th17 immunity, as seen in patients with IL-12Rβ1 deficiency (de Beaucoudrey et al., 2008). The poor response to IL-10 of the patients' leukocytes does not appear to be associated with the early-onset colitis seen in patients with AR IL-10, IL-10RA, or IL-10RB deficiencies (Engelhardt and Grimbacher, 2014; Engelhardt et al., 2013; Glocker et al., 2009; Glocker et al., 2011), possibly because of residual TYK2-independent responses to IL-10. Intriguingly, one patient (P-Ger) also had high serum IgE levels (Fuchs et al., 2016), whereas another (P-Jap) also had eczema and

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# Corneal Langerhans cells in children with celiac disease

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**Celiac disease (CeD) is a common small bowel enteropathy characterized by an altered adaptive immune system and increased mucosal antigen presenting cells. This study aims to establish if quantification of corneal Langerhans cells (LCs) using corneal confocal microscopy (CCM) could act as a surrogate marker for antigen presenting cell status and hence disease activity in children with CeD. Twenty children with stable CeD and 20 age-matched controls underwent CCM and quantification of central corneal total, mature and immature LC density. There was no difference in age (11.78 ± 1.7 vs. 12.83 ± 1.91; *P* = 0.077) or height (1.38 ± 0.14 vs. 1.44 ± 0.13; *P* = 0.125). BMI (18.81 ± 3.90 vs. 22.26 ± 5.47; *P* = 0.031) and 25 OHD levels (43.50 ± 13.36 vs. 59.77 ± 22.45; *P* = 0.014) were significantly lower in children with CeD compared to controls. The total (33.33(16.67–59.37) vs. 51.56(30.21–85.42); *P* = 0.343), immature (33.33(16.67–52.08) vs. 44.79(29.17–82.29); *P* = 0.752) and mature (1.56(0–5) vs. 1.56(1.04–8.33); *P* = 0.752) LC density did not differ between the CeD and control groups. However, immature (r = 0.535, *P* = 0.015), mature (r = 0.464, *P* = 0.039), and total (r = 0.548, *P* = 0.012) LC density correlated with age. Immature (r = 0.602, *P* = 0.038) and total (r = 0.637, *P* = 0.026) LC density also correlated with tissue transglutaminase antibody (Anti-TtG) levels assessed in 12/20 subjects with CeD. There was no difference in corneal LC density between children with CeD and controls. However, the correlation between corneal LC density and anti-TtG levels suggests a relationship with disease activity in CeD and requires further study.**

Celiac disease (CeD) affects ~ 0.7% of the world population[1], but may be more prevalent in the Middle East[2,3], especially in Qatar[4]. It is characterized by varying degrees of intestinal malabsorption, caused by an inappropriate immune response to ingested wheat gluten containing gliadin. Histopathological studies demonstrate villous atrophy with defective transepithelial[5,6] and paracellular uptake of gliadin by the intestinal mucosa of patients with active celiac disease.

Circulating dendritic cells are recruited to the inflamed mucosa in those with active CeD, and indeed , there is a significant increase in the number of dendritic cells (DC) in the lamina propria of patients with active celiac disease, which reverts to normal with a gluten-free diet[7,8]. DCs isolated from patients with active celiac disease behave as APCs and transcribe IFN-gamma[9], a key cytokine in the pathogenesis of CeD. The level of auto-antibodies to the enzyme transglutaminase 2 (TG2) and gliadin in gluten-consuming subjects are used as a diagnostic adjunct and marker of disease activity. Intriguingly, TG2 is expressed on most cell surfaces including monocytes and APCs, suggesting that it may facilitate the uptake of gluten[10].

Corneal Langerhans cells (LC's) are APCs which modulate the immune response in the cornea[11,12]. We have used corneal confocal microscopy (CCM) a rapid, non-invasive and well-tolerated ophthalmic imaging technique to quantify the number of mature and immature corneal LC's[11–15]. Moreover, we and others have shown increased LC's in patients with type 1 diabetes[11,16], latent autoimmune diabetes of adults (LADA)[16], multiple sclerosis (MS)[12], long-COVID[17], dry eye disease[18], systemic lupus erythematosus (SLE)[19], fibromyalgia[20], thyroid-associated ophthalmopathy[21], and chronic inflammatory demyelinating polyneuropathy (CIDP)[22]. These studies suggest that corneal immune cells are associated with a number of immune and inflammatory diseases.

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Brief report

# Biallelic TLR4 deficiency in humans

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**Background: Toll-like receptors (TLRs) mediate functions for host defense and inflammatory responses. TLR4 recognizes LPS, a component of gram-negative bacteria as well as host-derived endogenous ligands such as S100A8 and S100A9 proteins.**

**Objective: We sought to report phenotype and cellular function of individuals with complete TLR4 deficiency.**

**Methods: We performed genome sequencing and investigated exome and genome sequencing databases. Cellular responses were studied on primary monocytes, macrophages, and neutrophils, as well as cell lines using flow cytometry, reporter, and cytokine assays.**

**Results: We identified 2 individuals in a family of Qatari origin carrying a homozygous stop codon variant p.Q188X in TLR4 presenting with a variable phenotype (asymptomatic and inflammatory bowel disease consistent with severe perianal Crohn disease). A third individual with homozygous p.Y794X was identified in a population database. In contrast to hypomorphic polymorphisms p.D299G and p.T399I, the variants p.Q188X and p.Y794X completely abrogated LPS-induced cytokine responses whereas TLR2 response was normal. TLR4 deficiency causes a neutrophil CD62L shedding defect, whereas antimicrobial activity toward intracellular *Salmonella* was intact.**

**Conclusions: Biallelic TLR4 deficiency in humans causes an inborn error of immunity in responding to LPS. This complements the spectrum of known primary immunodeficiencies, in particular myeloid differentiation primary response 88 (MYD88) or the IL-1 receptor-associated kinase 4 (IRAK4) deficiency that are downstream of TLR4 and TLR2 signaling. (J Allergy Clin Immunol 2023;151:783-90.)**

***Key words:*** *Inflammatory bowel disease, primary immunodeficiency*

## INTRODUCTION

Identification of microbes via pattern recognition receptors is a key requisite for protective inflammatory immune responses. Toll-like receptors (TLRs) are a group of intracellular and extracellular transmembrane pattern recognition receptors.

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