

**Sidra Medicine**  
Pediatric Oncology  
Report 2022



# **SIDRA MEDICINE**

**PEDIATRIC ONCOLOGY REPORT 2022**



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# WELCOME MESSAGE



## **Dr. Wouter Hendrickx**

Lead Principal Investigator  
Pediatric Precision Oncology Program

## **Dr. Ayman Saleh**

Division Chief  
Oncology and Hematology Division

We are delighted to present the 2022 “Pediatric Cancer and Precision Oncology in Qatar” report; a joint update from the pediatric precision oncology program and the oncology and hematology division at Sidra Medicine.

Since opening its main hospital in 2018, Sidra Medicine has become the country’s sole healthcare provider for the care and treatment of children and young people with cancer. To support our personalized medicine strategy, we initiated the Sidra Medicine Pediatric Precision Oncology Program, which works

closely with our pediatric cancer services. This close synergy between our clinical and research divisions grants us a comprehensive understanding of our patients’ characteristics and epidemiology.

Our clinical and research collaboration also saw the birth of two important assets - the Pediatric Cancer Registry and The Sidra Pediatric Cancer Biorepository (SPCB). The former collects comprehensive clinical data, while the latter seeks consent from patients to donate materials no longer needed for diagnosis, thus enabling pertinent research for our local population.

Our programs, which are built on the expertise we have acquired over the years, have now become our springboard to precision oncology.

Worldwide, the incidence rates of childhood cancer range between 50 and 200 per million children. In Qatar, according to 2019 data, the pediatric cancer rate is 126 per million children. Our patient population at Sidra Medicine primarily consists of individuals of Arab and Asian descent, making up 70 percent and 25 percent of our patients, respectively. The most prevalent diagnoses are Leukemia (39%), Central Nervous System malignancies (14%), followed by Lymphoma, Germ cell tumors, Neuroblastoma, and Sarcomas.

As we improve the timing and rate of consent acquisition, we edge closer to providing molecular profiling at the point of diagnosis. This wealth of data - which surpasses current clinical requirements - is the result of our strategy to align people and technologies; ensuring harmony between pathology, research, and clinical care. This has been an equally challenging and rewarding endeavor.

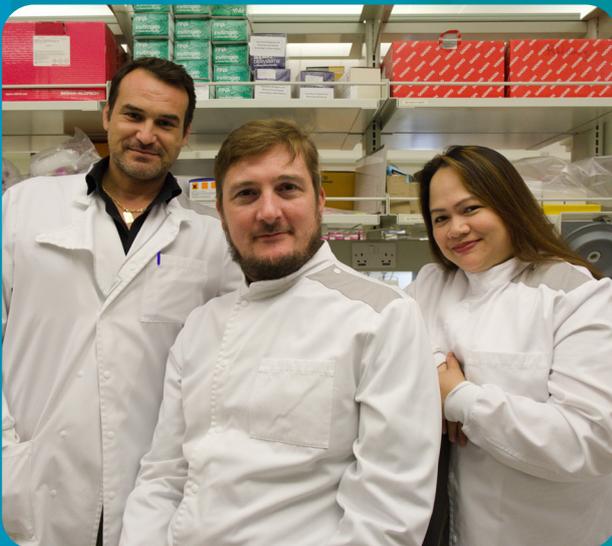
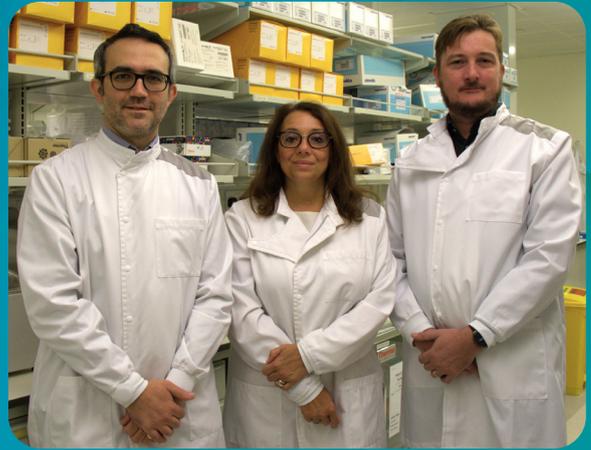
We firmly believe that our programs will empower pediatric patients to benefit from the seismic shift in cancer treatment, led by targeted and immunotherapy trials. This deeper understanding of patients' tumors - exploring genetic determinants, immune phenotypes, mutational load, or intratumoral heterogeneity - gives us insights into adapting groundbreaking therapies for our pediatric patients.

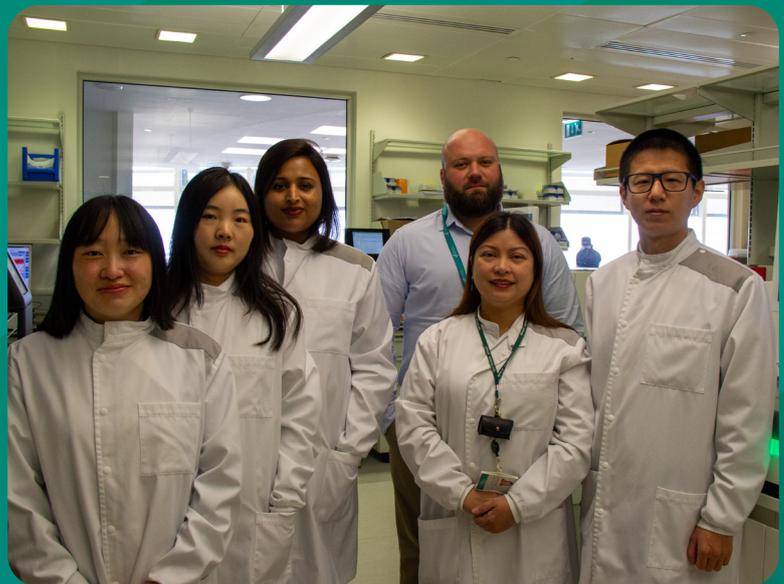
Through this report, we aim to share the rich data repository that guides our clinicians in identifying rare targetable somatic mutations, and in facilitating patient enrollment in worldwide clinical trials. The data allow us to spotlight novel molecular targets in specific patient subgroups, paving the way for new biomarkers and therapeutic strategies.

This work is at the forefront of personalizing precision medicine for every pediatric cancer patient in Qatar. It is our hope that this shared knowledge will enhance understanding and contribute to improved cancer care outcomes.



# MEET THE TEAM





# MEET THE TEAM

## CANCER RESEARCH INVESTIGATORS

Dr. Chiara Cugno, Dr. Wouter Hendrickx  
Dr. Cristina Maccalli, Dr. William Mifsud, Dr. Sara Deola

## NEUROSURGERY TEAM

Dr. Khalid Al-Kharazi, Dr. Ian Pople

## PATHOLOGY TEAM

Dr. William Mifsud, Dr. Erdener Ozer, Dr. Gordan Vujanic

## ONCOLOGY HEMATOLOGY TEAM

Dr. Ayman Saleh, Dr. Ata Maaz, Dr. Naima Al Mulla  
Dr. Chiara Cugno, Dr. Tayseer Al saad, Dr. Wafaa Abdelghani

## RESEARCH LAB TEAM

Dr. Christophe Raynaud, Dr. Sathiya Narayanan, Apryl Sanchez

## NURSING TEAM

Mohammed Anas, Rachel Park





## **PRECISION RESEARCH INFORMATION MANAGEMENT ENVIRONMENT (PRIME) TEAM**

Shafqat Baig, Mehshad Hamza

Mohammedhusen Khatib

## **GENOMICS CORE TEAM**

Lisa Sara Mathew, Li Liu, Kun Wang,

Guishuang Wang, Li Wang, Dr. Oleksandr Soloviov

## **CLINICAL RESEARCH COORDINATION**

Blessing Dason, Aisha Khalifa, Asma Jamil

## **BIOINFORMATICS TEAM**

Dr. Shimaa Sherif, Fazulur Vempalli,

Dr. Tariq Masoodi, Dr. Abdul Rahman Salhab,

## **LEAD PI OF THE PEDIATRIC PRECISION ONCOLOGY PROGRAM**

Dr. Wouter Hendrickx

## SPOTLIGHT: ROLE OF RESEARCH NURSES

Blessing has played a crucial role in setting up the database underpinning Sidra Medicine's Pediatric Cancer Biorepository and Pediatric Cancer Registry.



### **Blessing Dason**

Research Nurse and Clinical Informatics Specialist  
Sidra Medicine

“With my dual background in nursing and research, embarking on this Clinical informatics project was a unique and fascinating journey. I was constantly learning new codes, testing the database or the application, identifying required modifications, making the necessary changes, and then retesting. It’s been an engaging cycle of innovation and improvement. This is a process that I have deeply enjoyed, as it draws upon my interest and expertise in both medical science and technology.

I began my journey with the Biorepository

in November 2019 and have continued to work here since then, contributing to this groundbreaking endeavor in pediatric cancer care.

Setting up the Pediatric Biobank presented some interesting challenges, primarily because it was built from the ground up. The most significant challenge lay in validating the database. Identifying and rectifying each minor modification was a task that required intense focus and precision.

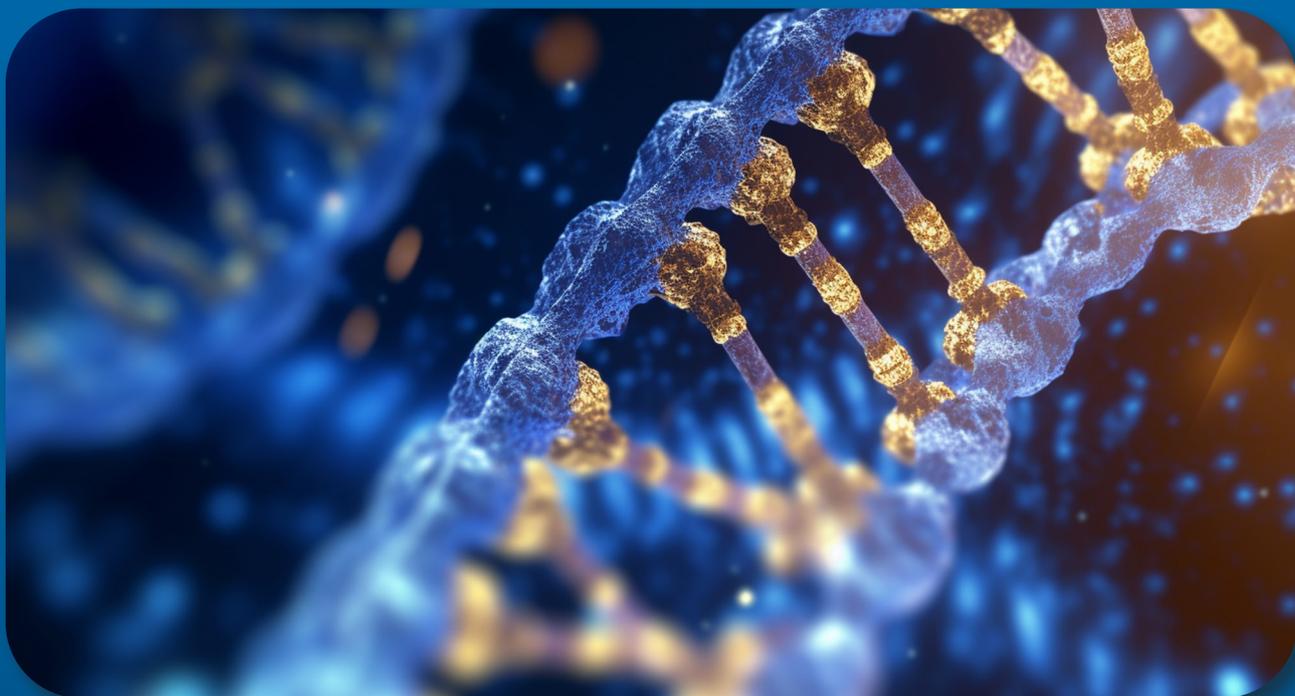
Once the database was finalized, we encountered

another hurdle: extracting data from Cerner. The data wasn't always directly accessible in Cerner, necessitating a complex extraction process. Additionally, I had to familiarize myself with various medical codes, such as ICD-10, ICD-O3, and HPO - which was a steep learning curve but critical for accurately interpreting and organizing our data.

Research nurses occupy a unique position, particularly when armed with a dual skill set like mine. Given my nursing background, I am well versed in medical terminologies and have a solid understanding of patient treatments and outcomes. This equips me to scrutinize patient data in a meaningful way for our research.

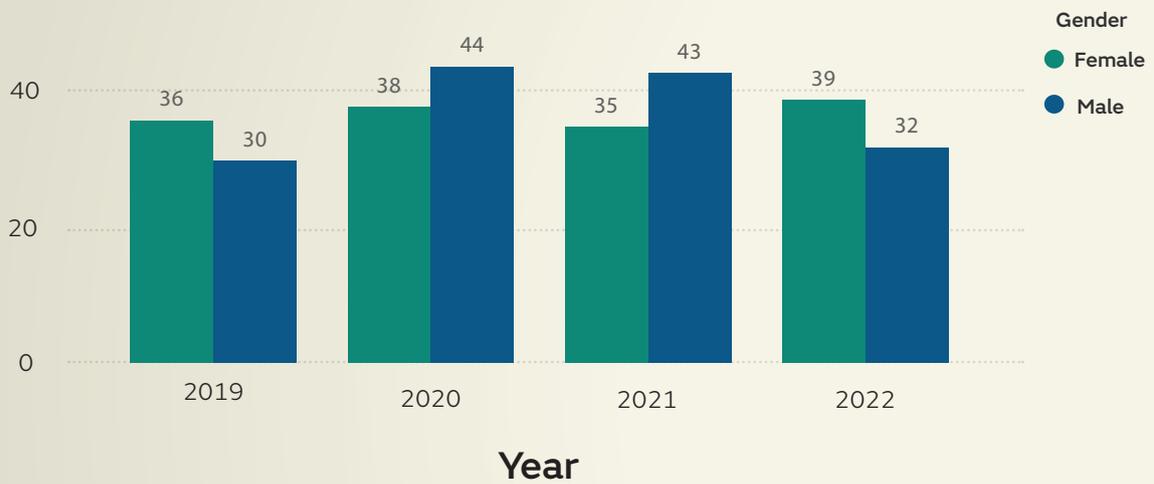
We contribute significantly to clinical research in several ways. We assist clinicians in obtaining informed consents; collecting research samples; entering patient data into the database; and validating this data. These tasks are particularly critical when dealing with oncology patients, as comprehending and extracting correct data can be quite challenging. Having research nurses in the team makes this process more manageable.

In essence, research nurses bridge the gap between patient care and research, leveraging our medical knowledge and experience to drive better health outcomes. It's about making every bit of patient information count, and utilizing this data to facilitate advancements in pediatric healthcare."

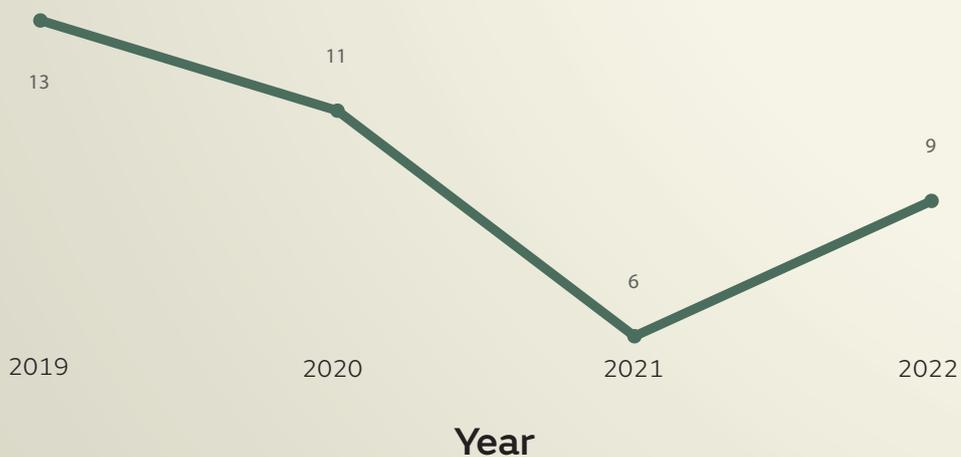


# SIDRA MEDICINE PEDIATRIC CANCER REGISTRY

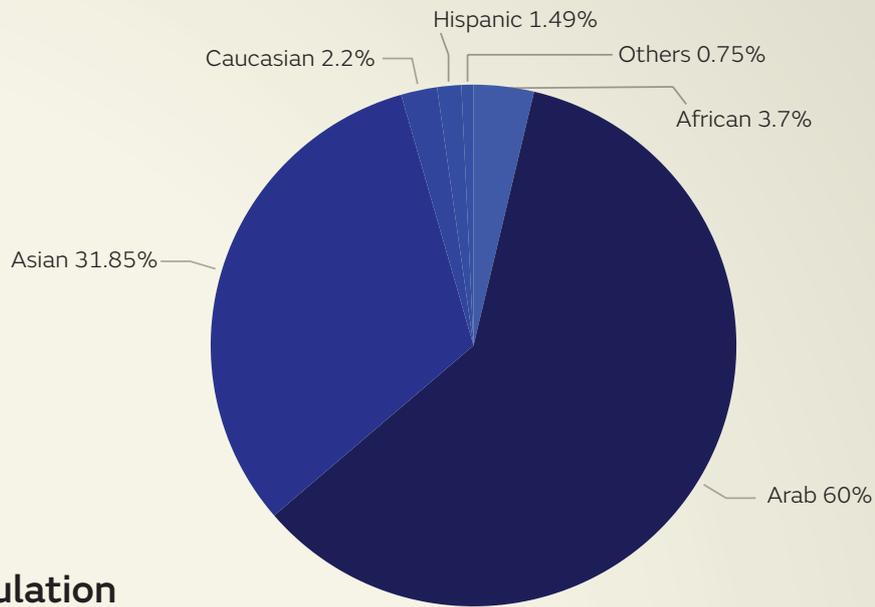
## Cancer Registry By Diagnosis Year



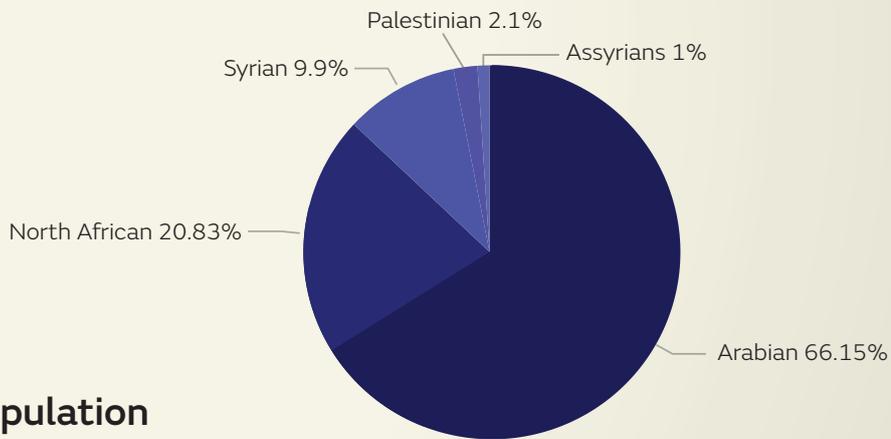
## Cancer Patients Treated Abroad By Year



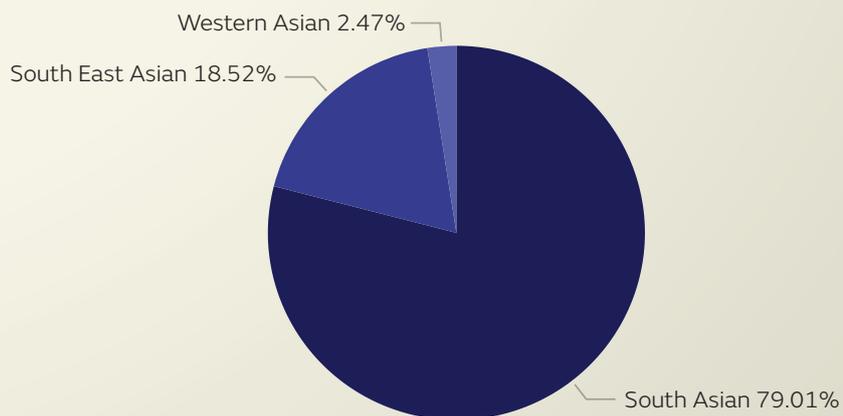
## Ethnicity Of Our Patients



## Arab Population



## Asian Population



## SPOTLIGHT: THE JOURNEY BEHIND UNDERSTANDING GENOMIC LANDSCAPE OF PEDIATRIC CANCER

Dr. Shimaa details the genomic landscape of pediatric cancers based on her PhD studies and bioinformatics and genomic expertise:

“Computational biologists play a crucial role in enhancing patient outcomes in pediatric cancer research. By leveraging our expertise in bioinformatics and computational analysis, we can significantly contribute to the development of personalized treatment strategies and advancements in precision medicine.

We analyze large-scale genomic and clinical datasets, identifying genetic alterations, tumor subtypes, and potential therapeutic targets. Through integrative analysis, we can uncover patterns and associations that may not be readily apparent, providing valuable insights into the underlying biology of pediatric cancers.

My active involvement in research, particularly in the field of bioinformatics analysis of pediatric cancer patients, began during my PhD studies in the pediatric cancer omics lab at Sidra Medicine, where I was privileged to work under the guidance of Dr. Wouter Hendrickx.

My research focus was dedicated to understanding the immunogenomics of pediatric solid tumors and identifying potential therapeutic targets. During this journey, we built a collaborative network with clinicians, researchers, and bioinformaticians. Together, we developed and implemented computational pipelines for analyzing large-scale genomic datasets, uncovering valuable insights into



**Dr. Shimaa Sherif**  
Computational Biologist  
Sidra Medicine

the molecular underpinnings of pediatric solid tumors. Setting up the Sidra Pediatric Cancer Biobank was fraught with several challenges, particularly from the analysis perspective. One of the most significant issues was the rarity of Pediatric Cancer. Pediatric cancer is relatively rare compared to adult cancer, which makes it difficult to collect a sufficient number of samples from each tumor type. This scarcity of samples can limit the statistical power and generalizability

of our research findings. Compounding the problem is the lack of large-scale, multi-omics online cohorts specific to pediatric solid tumors, which are readily available for some adult cancers.

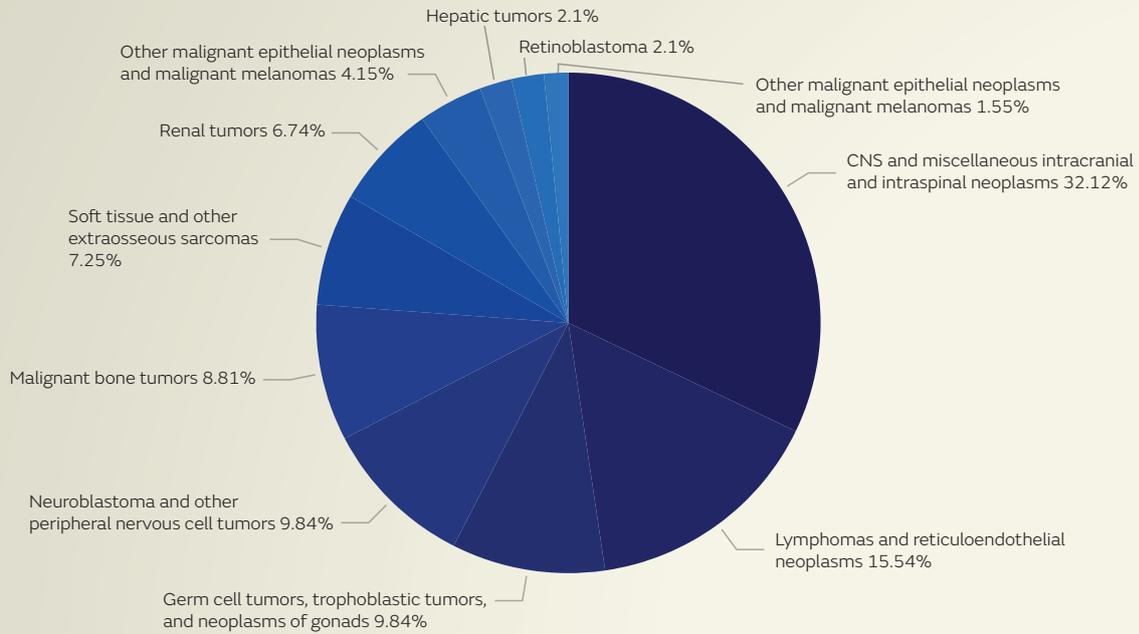
Having access to comprehensive datasets containing detailed clinical and genomic information from a significant number of pediatric cancer patients could greatly enhance our research efforts. Unfortunately, such resources are limited in the pediatric cancer field, which restricts our ability to leverage existing data for analysis. We also faced the challenge of the inherent heterogeneity of Pediatric Solid Tumors. These tumors encompass a diverse range of diseases with distinct genetic and molecular characteristics. This heterogeneity added another layer of complexity when setting up the biobank. To ensure representative sampling across various tumor types, we had to forge extensive collaborations and coordination

with multiple hospitals and research centers. Moreover, sample collection was a significant issue. Ethical considerations and the need to minimize invasiveness make collecting samples from pediatric cancer patients particularly challenging. Invasive techniques required for obtaining samples from specific parts of the body may be more difficult to perform in pediatric patients. These challenges can limit the availability and diversity of samples in the biobank, potentially affecting the representation of certain tumor types.

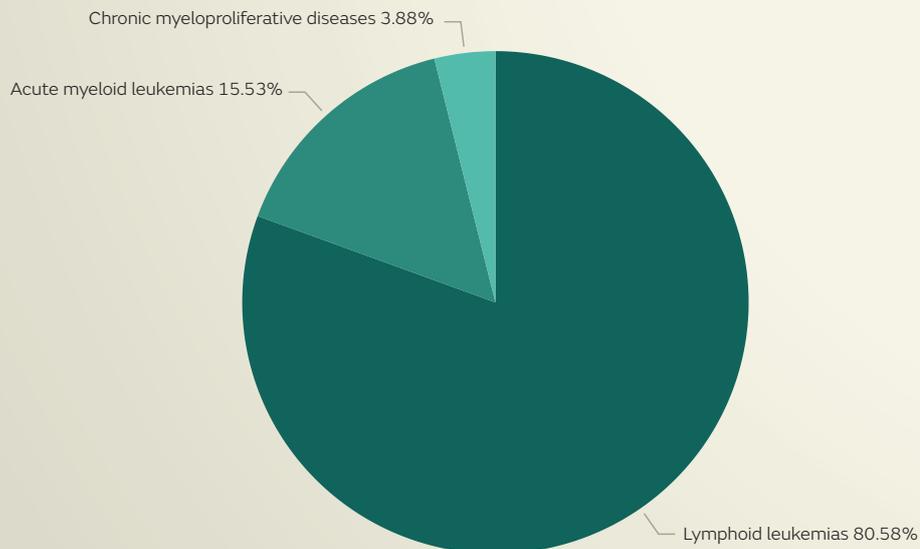
To overcome these obstacles, we adopted a multidisciplinary approach. We collaborated with pediatric oncologists, research institutions, and relevant stakeholders, aiming to address these challenges and create a valuable resource for advancing our understanding of pediatric solid tumors and improving patient outcomes.”



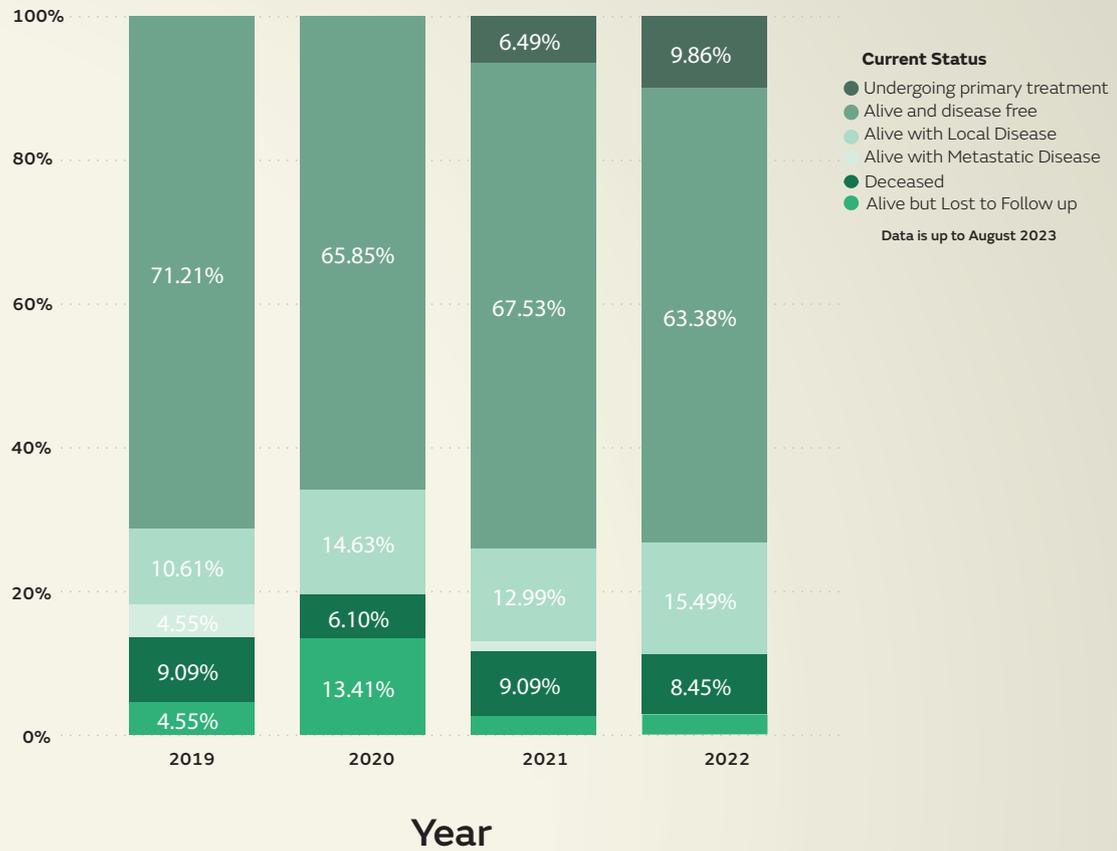
## Types of Pediatric Solid Cancer Presented at Sidra Medicine 2019 - 2022 (67%)



## Types of Pediatric non- Solid Cancer Presented at Sidra Medicine 2019 - 2022 (33%)



## Current Status of Pediatric Cancer Patients



## Patients with Metastasis at Diagnosis



# SPOTLIGHT: UNMASKING PEDIATRIC CANCER

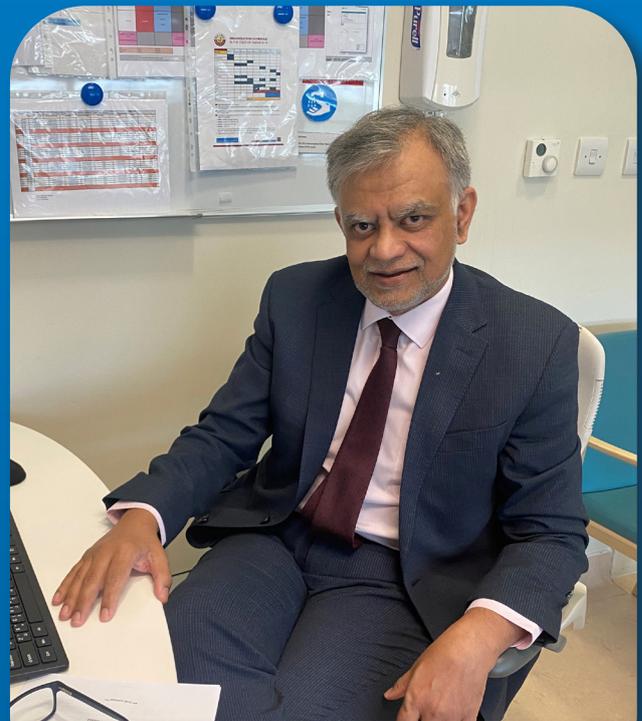
Dr. Ata Maaz, is an important member of our groundbreaking Pediatric Precision Oncology Program and discusses its impact:

“At Sidra Medicine, we see and treat a significant number of pediatric cancer cases— around 60-70 newly diagnosed children every year. In general, pediatric cancer cases have significantly better treatment outcomes compared to adult cancers. However, for a long time, we didn't fully understand the reason behind this differential. The presumption was that it might be due to our ability to deliver more intensive treatments to children and their better tolerance towards these treatments. Interestingly, with the evolution of our understanding of the genetic underpinnings of cancer, we're starting to unearth some important insights.

Pediatric cancers might actually possess biological differences from their adult counterparts—even when the anatomical and histological appearances seem very similar. This realization, though complex, opens up new avenues for research and targeted treatments. Precision Oncology studies, such as the one we're engaged in here, have the potential to not just underscore these differences but to use this knowledge to revolutionize treatment protocols and significantly improve patient outcomes.

Each patient is unique and their care and case, illuminates different aspects of the scientific, personal, familial, or social facets of the battle against cancer.

One of my recent patients, a 5-year-old boy, was diagnosed with a very rare brain tumor. Technically categorized as a 'low-grade' cancer, this type of



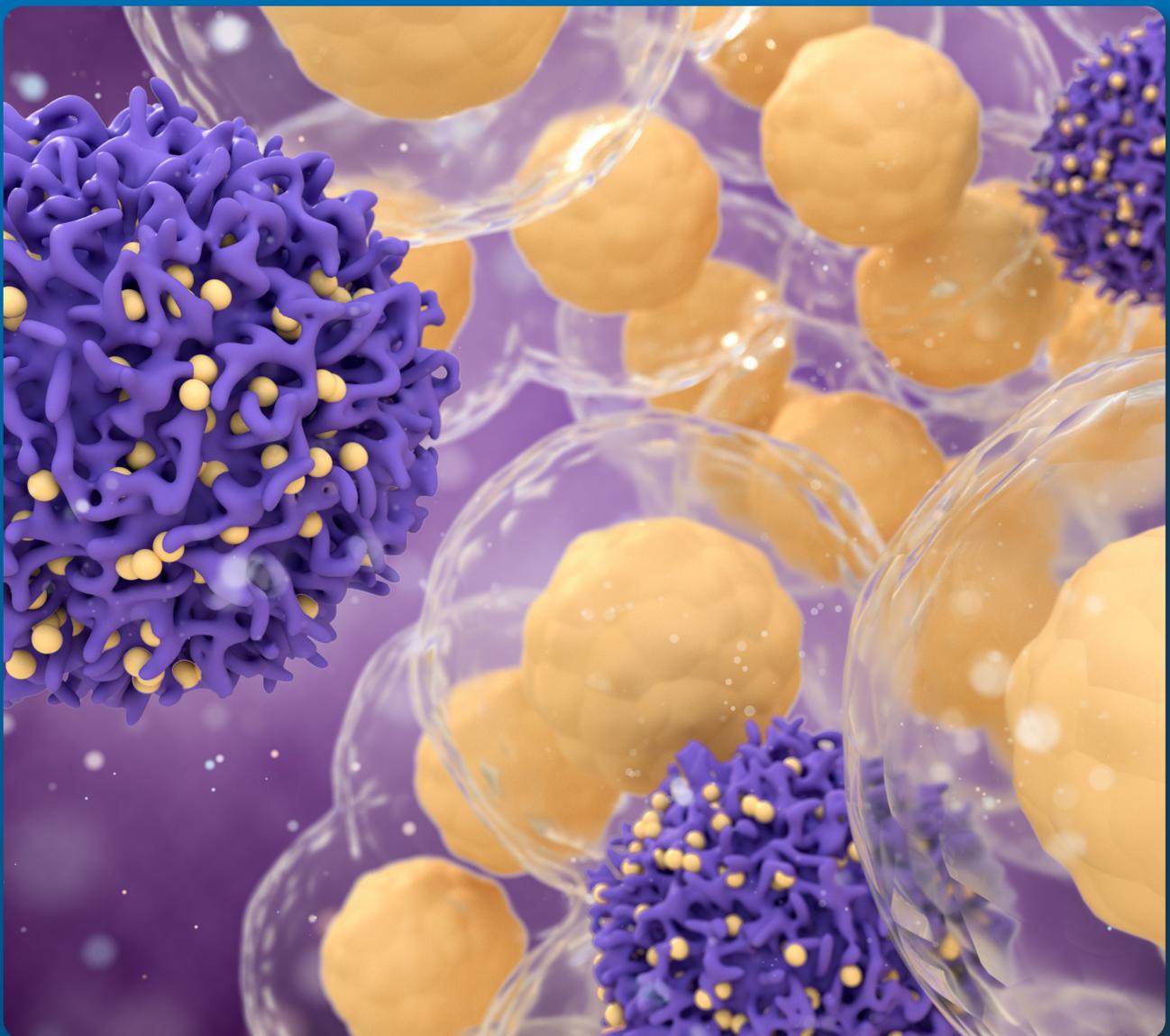
**Dr. Ata Ur Maaz**

Senior Attending Physician (Oncology)  
Sidra Medicine

tumor can, however, have a severe impact on a patient's life—as was the case with this young boy. Diagnosis in such cases is challenging, but what's even more intricate is identifying the correct treatment modality that strikes a balance between achieving an adequate response and maintaining a good quality of life for the patient. This patient's diagnosis was facilitated by Sidra Medicine's cutting-edge neuro-radiology and neurosurgery capabilities, combined with detailed anatomical pathology studies.

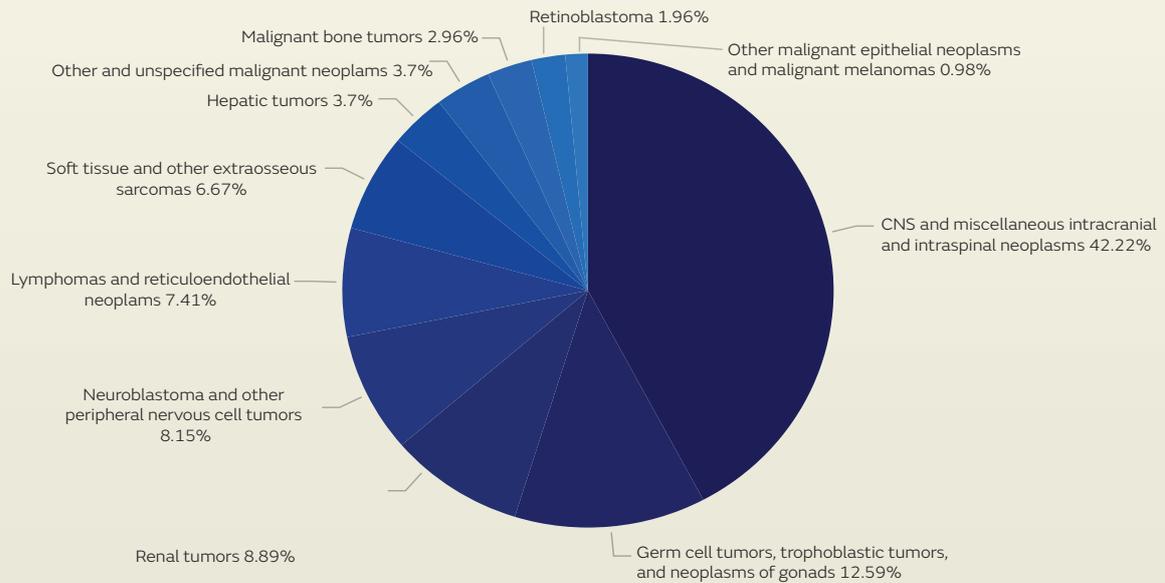
These initial findings were then validated by molecular diagnostic tests that have recently been established as part of our continual advancement in medical technology. In a wonderful turn of events, these tests not only confirmed the diagnosis but also helped us identify a 'target' against which a new class of drugs had shown efficacy. The boy is now on this targeted treatment, and we are fervently hoping for an adequate response to this approach.

It's important to mention that studies like the one we're engaged in can play a monumental role in identifying such treatment targets and contributing to the development of newer, more effective drugs and treatment protocols. This is the potential of medical research and progress in the realm of pediatric oncology which is a potential we are constantly striving to fulfill."

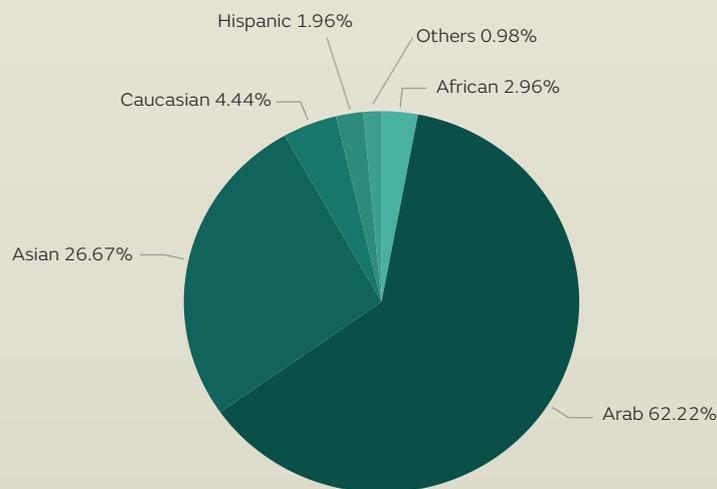


# BIOBANK DATA

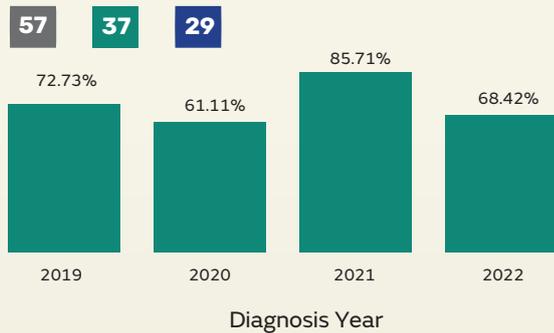
## Types of Pediatric Cancer Included in the Sidra Medicine Biobank



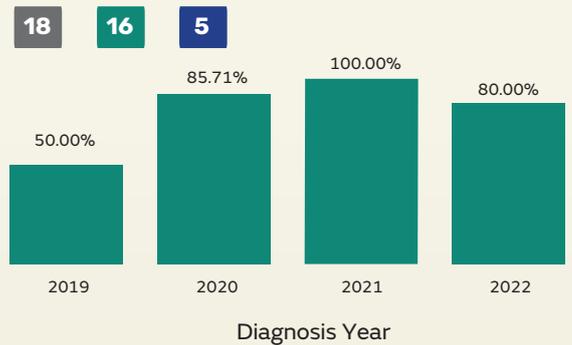
## Biobank Ethnicity



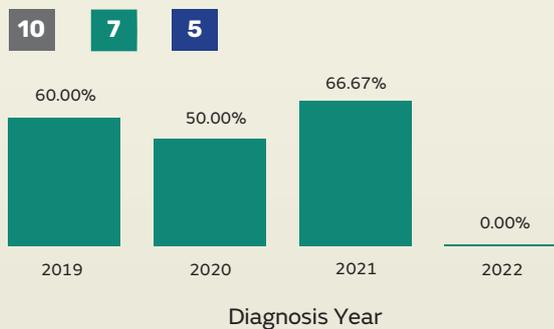
### Consent rate for CNS and intracranial and intraspinal neoplasms



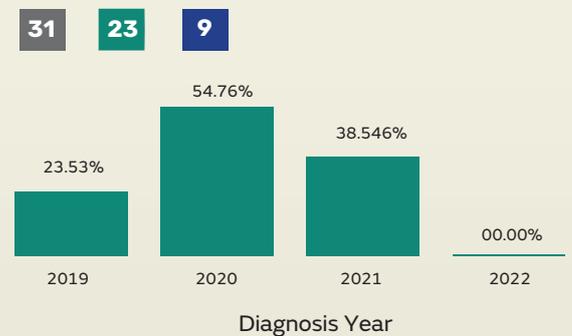
### Consent rate for Germ cell tumors, trophoblastic tumors, and neoplasms



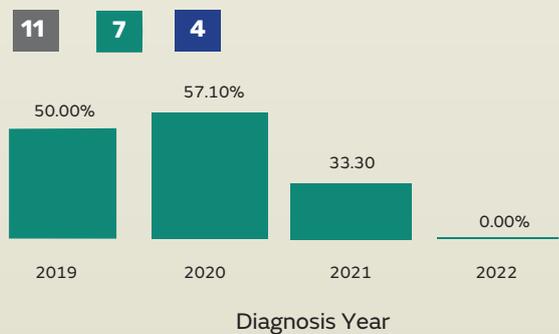
### Consent rate for Soft tissue and other extrasosseous sarcomas



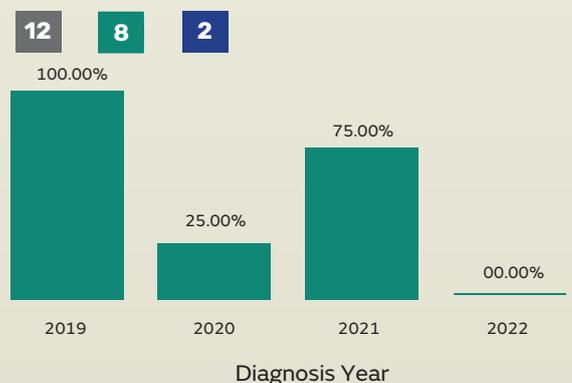
### Consent rate for Other solid tumors



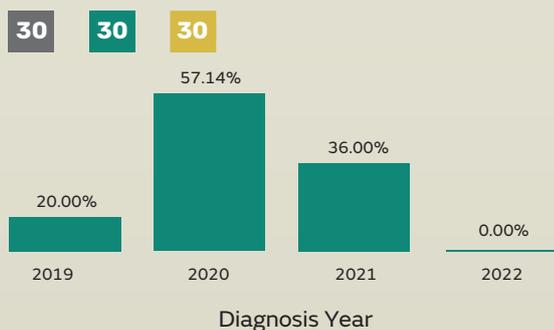
### Consent rate for Neuroblastoma and other peripheral nervous cell tumors



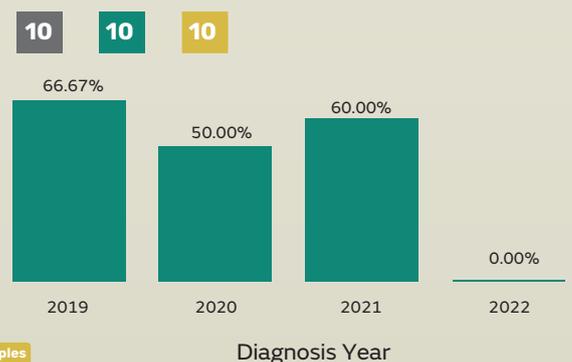
### Consent rate for renal tumors



### Consent rate for Lymphoid leukemias



### Consent rate for Acute myeloid leukemias



Total Consented Patients Available Blood Samples Available Tumour Samples Available Bone Marrow Samples

Data is up to August 2023

# SPOTLIGHT: THE ROLE OF PEDIATRIC PATHOLOGY

Dr. William Mifsud talks about the collaborative spirit at Sidra Medicine and how his role in clinical pathology and active research, can bridge scientific discoveries in the lab and their practical application at the bedside:



**Dr. William Mifsud**  
Attending Physician (Anatomical Pathology)  
Sidra Medicine

“The role of a pathologist is critical in the diagnostic process, especially when it comes to diseases like cancer. Most, if not all, cancer diagnoses require a tissue diagnosis made by a pathologist. This meticulous work allows us to guide the treatment that is most appropriate for each individual patient. It’s this initial step that sets the course for the entire treatment journey. In a research setting, this principle extends further.

I view my role as a pediatric pathologist in a leading children’s hospital like Sidra Medicine as a distinctive privilege. Here, we are surrounded by an expansive

and dynamic research community, which is an integral part of our ecosystem. Over the years, I’ve had the opportunity to involve myself in a multitude of research projects. But those that have always piqued my interest are tied to pediatric cancer research. It’s a field that is continually evolving, offering new insights into the disease, and I’m proud to contribute to this important body of knowledge.

What resonates with me the most about working at Sidra Medicine, is the powerful sense of teamwork that permeates every aspect of our work. We have

cultivated an environment where integration is key from the consultation rooms of the clinic to the technical quarters of my diagnostic laboratory, right up to the buzzing hub of the research laboratories. It's been an honor to have played a part in establishing this collaborative team along with my esteemed colleagues, all of whom are driven by a shared vision of pushing the boundaries of pediatric healthcare.

Being a part of a collaborative team is not only about understanding our research findings but to contextualize these findings within the unique clinical scenario of each patient. It's about connecting the dots between our scientific discoveries in the lab and their practical application at the bedside. But our work doesn't stop there.

In the longer term, we delve into retrospective analysis, studying how our patients responded to their treatment. This isn't merely a process of review; it's a learning curve, an opportunity to glean insights on what worked, what didn't, and why. It's through this systematic evaluation that we continue to refine our strategies, paving the way for improved treatment protocols for future patients.

Thus, as a clinical research pathologist, my role becomes instrumental in the continuous cycle of learning and improving in pediatric healthcare. It's about linking research and practice, learning from every patient, every case, and leveraging this knowledge to drive better health outcomes not only for our current patients but for generations to come."

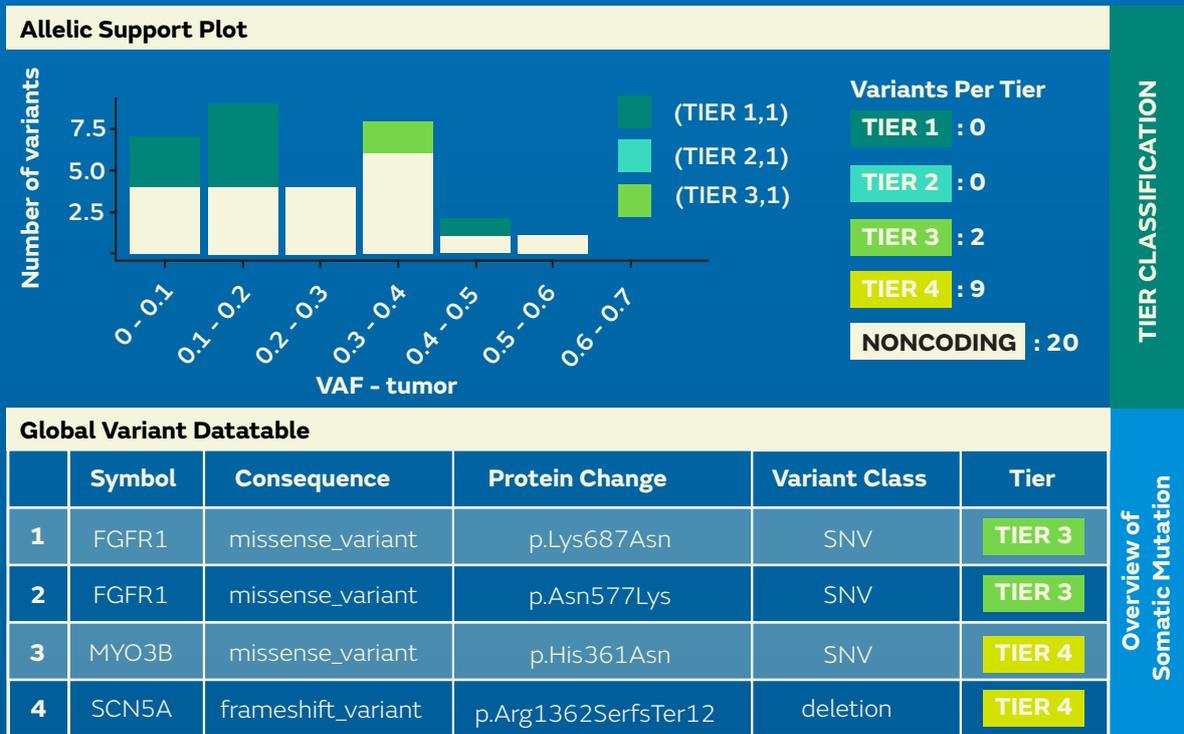


# PATIENTS' REPORTS

## 1- Personal Cancer Genome Reporter (PCGR)

Somatic mutations are changes to a person's DNA that occurs after conception to any cell that isn't a germ cell (egg or sperm cell). Somatic or acquired genomic variants are the most common cause of cancer. In the SPCB, we are generating a PCGR report for each patient that interprets both somatic SNVs/InDels and copy number aberrations. The prioritization of SNV and InDels found in the tumor sample is done according to a four-tiered structure, adopting the joint consensus recommendation by Association for Molecular Pathology and American College of Medical Genetics and Genomics.

- A) Tier 1: Variants of strong clinical significance - constitutes variants linked to predictive, prognostic, or diagnostic biomarkers.
- B) Tier 2: Variants of potential clinical significance - constitutes other variants linked to predictive, prognostic, or diagnostic biomarkers.
- C) Tier 3: Variants of uncertain clinical significance - includes other coding variants found in oncogenes or tumor suppressor genes.
- D) Tier 4: includes other coding variants.



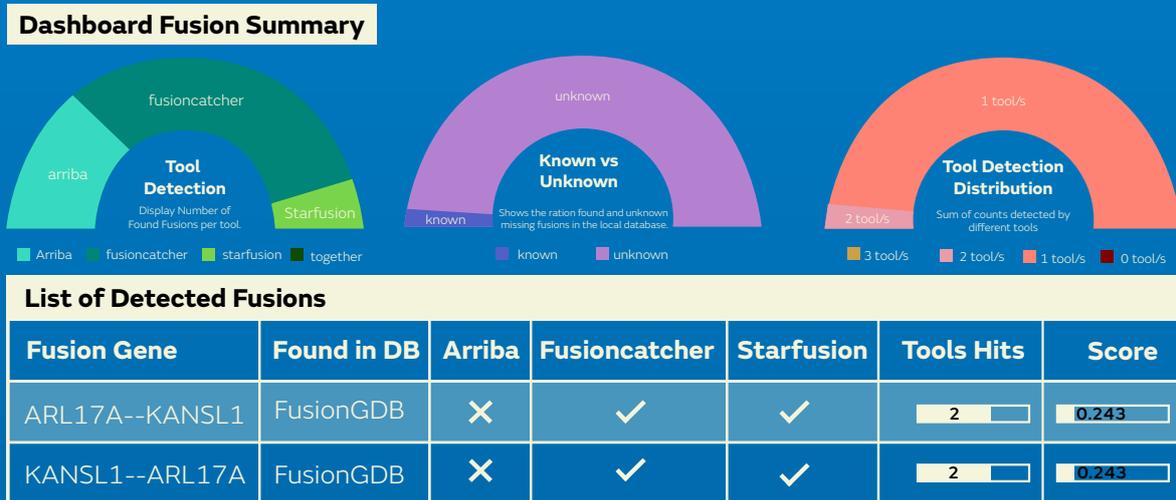
The PCGR include relevant ongoing or future clinical trials, focusing on studies with molecularly targeted interventions.

Molecularly Targeted Trials							
	NCT ID	TITLE	OVERALL STATUS	CONDITION	KEYWORD	INTERVENTION	PHASE
1	NCT02887040	Study of Antineoplaston Therapy + Radiation vs. Radiation Only in Diffuse, Intrinsic, Brainstem Glioma	Not Yet Recruiting	Brainstem glioma	Radiotherapy	Antineoplaston A10, Antineoplaston AS2-1	3
2	NCT04425798	Connectivity Alterations After Levetiracetam Application	Not Yet Recruiting	glioma	Radiotherapy		
3	NCT02432417	The Addition of Chloroquine to Chemoradiation for Glioblastoma	Not Yet Recruiting	Glioblastoma	Chemoradioheraphy Immunotherapy Radiotherapy	Chloroquine	2

Clinical trials for these mutations

## 2- Fusion reports

A **fusion gene** is defined as two genes that are joined so that they are transcribed and translated as a single unit. Fusion proteins produced by this change may lead to the development of some types of cancer. For the SPCB, we are generating a fusion report for each patient through implementing a bioinformatics analysis pipeline for RNA sequencing using list of tools for detecting and visualizing fusion genes.



## 3- Cancer Predisposition Sequencing Reporter (CPSR)

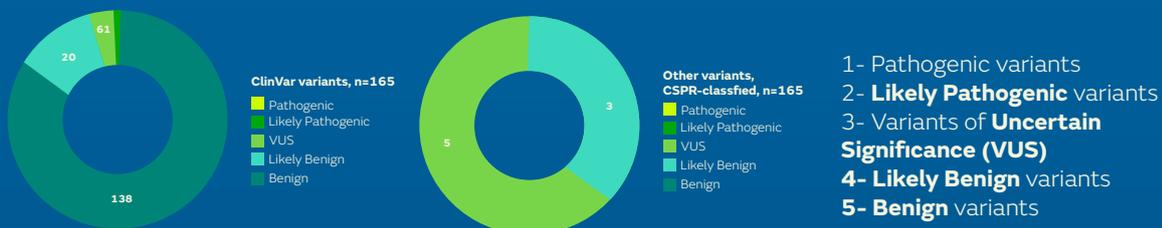
**Cancer predisposition gene is a term** used to describe a gene that may increase a person's risk of developing some types of cancer if it has certain mutations (changes).

For the SPCB, we are generating a CPSR for each patient. The CPSR is a computational workflow that interprets and classifies germline DNA variants identified from next-generation sequencing in the context of cancer predisposition and inherited cancer syndromes.

### Variants Classification

Pathogenic variant is a genetic alteration that increases an individual's susceptibility or predisposition to a certain disease or disorder.

Variants are classified based on the pathogenicity into different classes ordered by highest pathogenicity:



**Likely Pathogenic Variant Detected in One of SPCB Patients**

SYMBOL	CLINVAR PHENOTYPE	CONSEQUENCE	PROTEIN CHANGE	GENOTYPE
MUTYH	Colon cancer; Endometrial cancer; Hereditary cancer -predisposing syndrome; Neoplasm of stomach; Pilomatricoma; Breast carcinoma; Carcinoma of colon; Small intestine carcinoid; MYH-associated polyposis; Ovarian carcinoma; Colorectal adenomatous polyposis, autosomal recessive, with pilomatricomas; not specified; not provided	missense_variant, splice_region_variant	p.Gly368Asp	heterozygous

## SPOTLIGHT: CHAMPIONING HOPE FOR CANCER PATIENTS

**Dr. Hadi Rasheed talks about the role of Qatar Cancer Society and its collaboration with Sidra Medicine in improving the lives of children dealing with cancer:**

“Qatar Cancer Society plays a crucial and compassionate role in improving the lives of children dealing with cancer and their families. Pediatric cancer patients face unique challenges, and we tailor our programs to their needs. The financial burden of cancer treatment can be immense. Qatar Cancer Society provides vital financial aid, easing this burden and ensuring access to advanced treatments that might otherwise be out of reach. We also fund medical equipment, aids, and prosthetics, creating a more comfortable treatment environment.

We also provide a safe space for children and their families to connect with others facing similar challenges, countering the isolation often linked to the disease. Emotional well-being is vital for these young fighters. Activities like art therapy, music therapy, and play therapy offer valuable support during treatment. By collaborating with Sidra Medicine, we direct funds to research projects specifically focused on pediatric cancers, aiming to ease the challenges for both children and their families. We also advocate for increased government funding and attention toward childhood cancers.

As the Scientific Advisor and Head of the Cancer Awareness and Professional Development Department, I orchestrate events, seminars, and workshops to share vital information about different cancers. This includes educating the



**Dr. Hadi Mohamad Abu Rasheed**  
Head of Cancer Awareness and  
Professional Development Dept.  
Qatar Cancer Society

ensuring access to insights and financial aid.

Our support includes providing families with resources to navigate the complexities of a cancer diagnosis. We organize outings and events to give children with cancer moments of normalcy, relaxation, and joy. We have also partnered with Uber, to provide transportation services for cancer patients, ensuring easy access to treatment centers.

We have collaborative campaigns with

Sidra Medicine, to highlight pediatric cancers, advocating for better policies, funding, and providing support at various levels. These initiatives underscore our commitment to enhancing the lives of these young fighters.

Supporting conferences, workshops, and symposiums organized by Sidra Medicine also fosters the exchange of knowledge among experts. By raising awareness about the unique research needs of childhood cancer, we aim to influence public opinion, driving policy changes and funding priorities. Our direct connection with cancer patients and their families acts as a bridge, offering invaluable real-world insights to researchers and steering their work toward addressing patients' needs.

As a result, Qatar Cancer Society has emerged as a trailblazer in advancing cancer research in recent years.

Our unwavering commitment is evident through substantial funding for collaborative research ventures. These initiatives often target areas that might be overlooked or underfunded elsewhere.

Our contributions extend beyond scientific research, encompassing studies that improve quality of life and explore public perceptions of cancer. We have the power to bring together diverse researchers from different institutions, specialties, and even countries to collaborate, spurring joint efforts to propel cancer research forward.

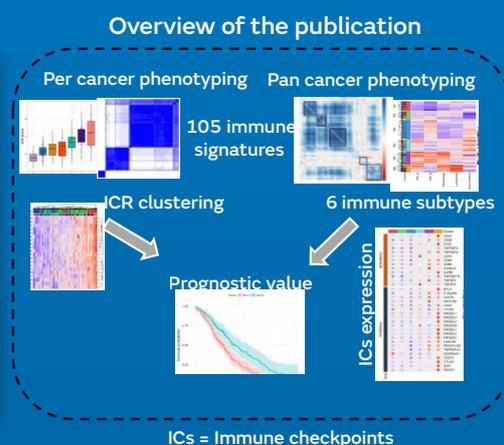
At Qatar Cancer Society, we envision a future where every cancer diagnosis is tailored meticulously to the individual, resulting in precise, effective, and compassionate treatments. We believe in multidisciplinary collaboration and the advancement of precision medicine techniques to enhance patient outcomes and experiences."

# PUBLICATION HIGHLIGHT

*In May 2022 our team published the immune landscape of solid pediatric tumors paper.*

## The Immune Landscape of Solid Pediatric Tumors

Shimaa Sherif, Jessica Roelands, William Mifsud, Eiman I. Ahmed, Christophe M. Raynaud, Darawan Rinchai, Abbirami Sathappan, Ata Maaz, Ayman Saleh, Erdener Ozer, Khalid A. Fakhro, Borbala Mifsud, Vésteinn Thorsson, Davide Bedognetti & Wouter R. L. Hendrickx



In this study, we analyzed data from pediatric tumors to understand the role of the immune system in these diseases. We focused on five types of tumors: Wilms tumor, neuroblastoma, osteosarcoma, clear cell sarcoma of the kidney, and rhabdoid tumor of the kidney.

Using advanced bioinformatics pipelines, we assessed the performance of the Immunologic Constant of Rejection (ICR), which captures the immune response against the tumor. We also analyzed the expression of genes related to the immune system and identified different immune subtypes within the tumors.

The results revealed interesting insights. In osteosarcoma and high-risk neuroblastoma cases without MYCN gene amplification, a higher ICR score was associated with better survival. However, in Wilms tumor, a higher ICR score correlated with poorer survival.

By clustering the immune traits, we identified six distinct immune subtypes among pediatric patients. The subtype with high infiltration of Th1 cells showed the best overall survival.

These findings suggest that pediatric tumors can be classified based on their immune characteristics, showing similarities to adult tumors. We propose that exploring immunological parameters could help refine diagnostic and prognostic biomarkers and identify tumors that might respond well to immune-based therapies.

This study contributes to our understanding of the immune landscape of pediatric tumors and opens up possibilities for improving treatment strategies and patient outcomes in the future.

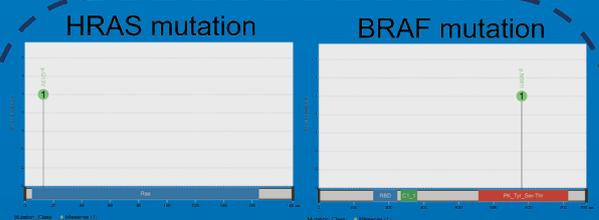
## Recent Case Report

# Identification of unusual actionable mutations through genomic profiling in a child with an aggressive sarcoma.

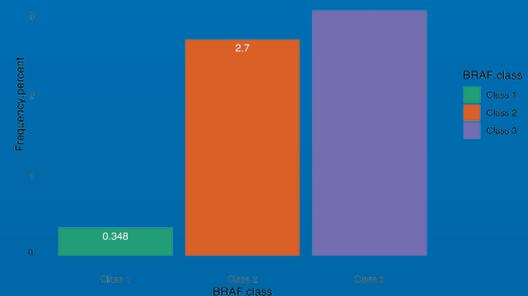
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### Case presentation

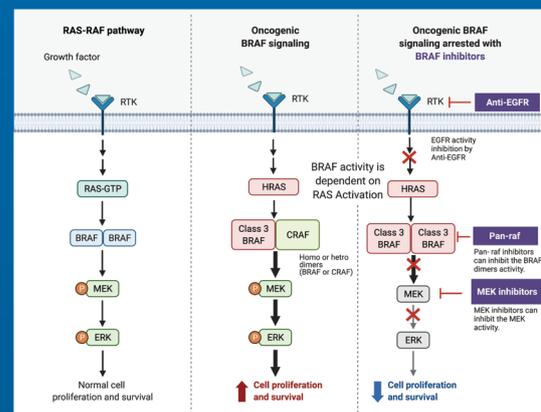
A 3-year-old male child was diagnosed with embryonal rhabdomyosarcoma (ERMS) of the neck at Sidra Medicine. Initial stage-based chemotherapy resulted in tumor progression. Unexpectedly, we identified somatic mutations in two genes of the RAS/MAPK pathway (BRAF and HRAS), which are classically mutually exclusive. A clinical-grade NGS was performed that confirmed both mutations. The identified BRAF mutation (N581I) is a non-classical (Class III) hot-spot mutation, that has not been previously reported in ERMS. Class III BRAF mutations are a novel group of mutations characterized by the induction of a low tyrosine kinase activity and require coexistent mechanisms for maintaining RAS activation through feedback mechanisms. While our patient has subsequently achieved complete remission following intensified treatment, the risk of relapse remains high and this information might be considered for therapeutic decision at further relapse/progression.



High frequency of co occurrence of HRAS with class III BRAF mutations in TCGA.



### RAS signaling pathway



Here we are reporting for the first time to our knowledge the co-occurring of BRAF and HRAS mutations in an RMS patient. The hypothesized biological rationale of this combination is the dependence of class III BRAF mutation (Asn581Ile) on Ras activation as postulated previously. Identifying BRAF alterations in pediatric cancers is critically important as therapeutic agents targeting BRAF or MEK may be incorporated into the clinical management of these patients.

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