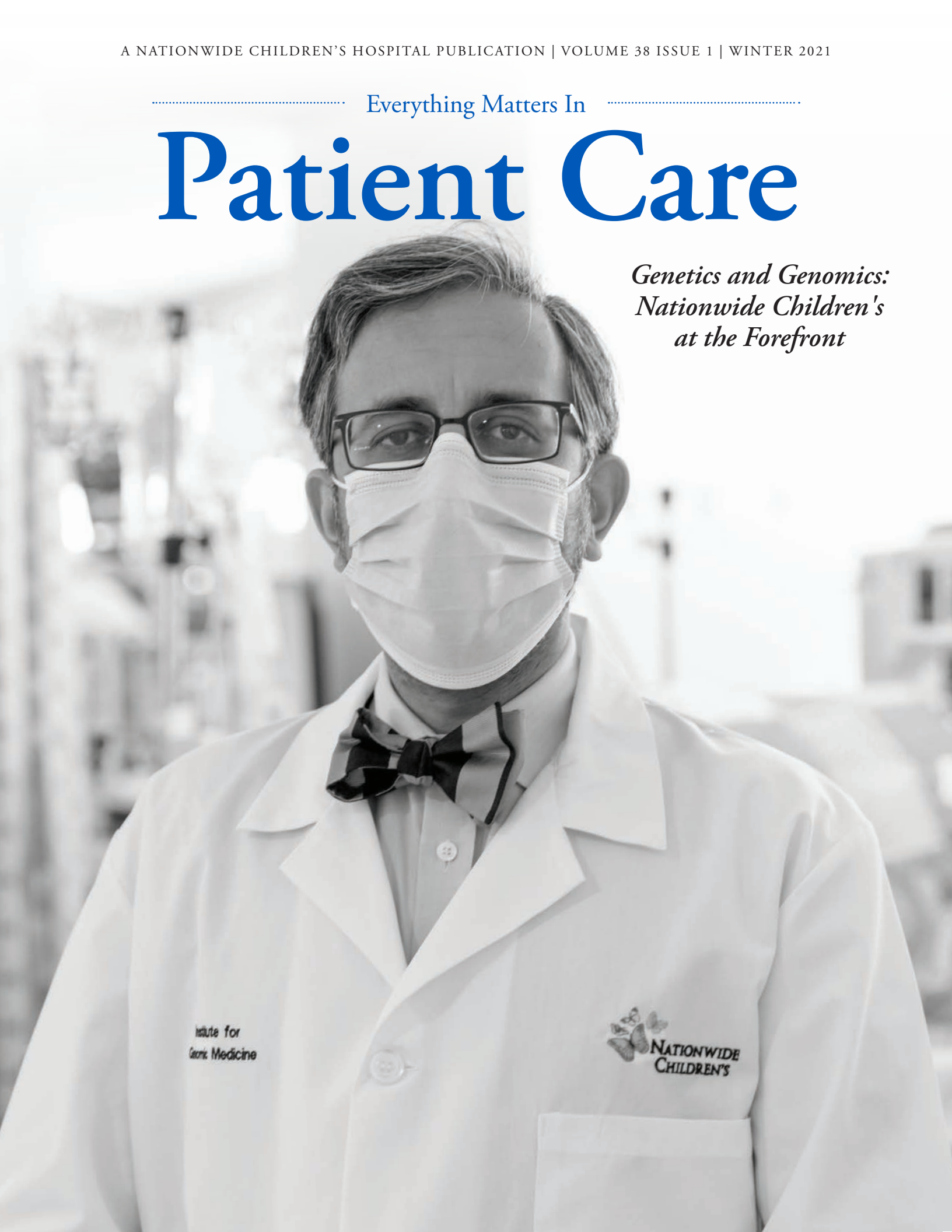
A NATIONWIDE CHILDREN'S HOSPITAL PUBLICATION | VOLUME 38 ISSUE 1 | WINTER 2021

Everything Matters In

Patient Care

Genetics and Genomics: Nationwide Children's at the Forefront



Bimal Chaudhari, MD, MPH,
uses rapid genome sequencing to create Best Outcomes for patients.

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Where Passion Meets Purpose

Lee Ann Wallace
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As part of the 2017-2022 Strategic Plan, Nationwide Children's Hospital committed to *Best Outcomes* for all children. This commitment includes developing cures for rare diseases and a better understanding of the treatment of genetic conditions in children.

Genomics is one of the areas of focus that we believe will accelerate our *Journey to Best Outcomes*. At the Abigail Wexner Research Institute at Nationwide Children's Hospital, our world-renowned research teams are breaking new ground in genomics, gene therapy, and tissue engineering. This research will provide transformational work in understanding the genetic causes of disease, an ability to more rapidly sequence genomes, as well as reducing the cost of this state-of-the-art medical science and technology.

Rather than a one size fits all approach, individualized treatment care plans can be developed using high precision diagnostics. Large research studies are taking place on the identification of cancer tumor DNA while understanding what processes cause a normal cell to become a cancer cell. Developing a better understanding of the cancer location and causes of these over-expressed genes, we will increase our successful outcomes for cancer therapies. The ability to translate their research into treatment using whole-exome sequencing allowing for diagnosis of pediatric conditions that traditional tests and investigation would not be able to identify. Through genome sequencing, targeted therapies, and medications based on the identification of genetic errors will be developed, all leading to improved outcomes.

While work has been focused on rare genetic conditions and cancer, the future is wide open. Other areas of future expansion include diagnosis and treatment of seizure disorders and the ability for rapid identification of neonatal conditions. As care team providers, we need to continue to expand our knowledge and understanding of genomics in our own areas of practice, while identifying the impact of these discoveries on our patients and their families.

The Steve and Cindy Rasmussen Institute for Genomic Medicine: An Overview

Richard K. Wilson, PhD, Executive Director, The Steve and Cindy Rasmussen Institute for Genomic Medicine, The Abigail Wexner Research Institute at Nationwide Children's Hospital
Elaine R. Mardis, PhD, Co-executive Director, The Steve and Cindy Rasmussen Institute for Genomic Medicine, The Abigail Wexner Research Institute at Nationwide Children's Hospital

When Nationwide Children's Hospital leadership completed their strategic planning process in 2013, they identified genomics as an accelerator for the hospital that would differentiate its health care in significant and impactful ways as compared to other children's hospitals. What is genomics and why was it considered a critical accelerator? How did this aim of the strategic plan manifest itself and what has happened since then?

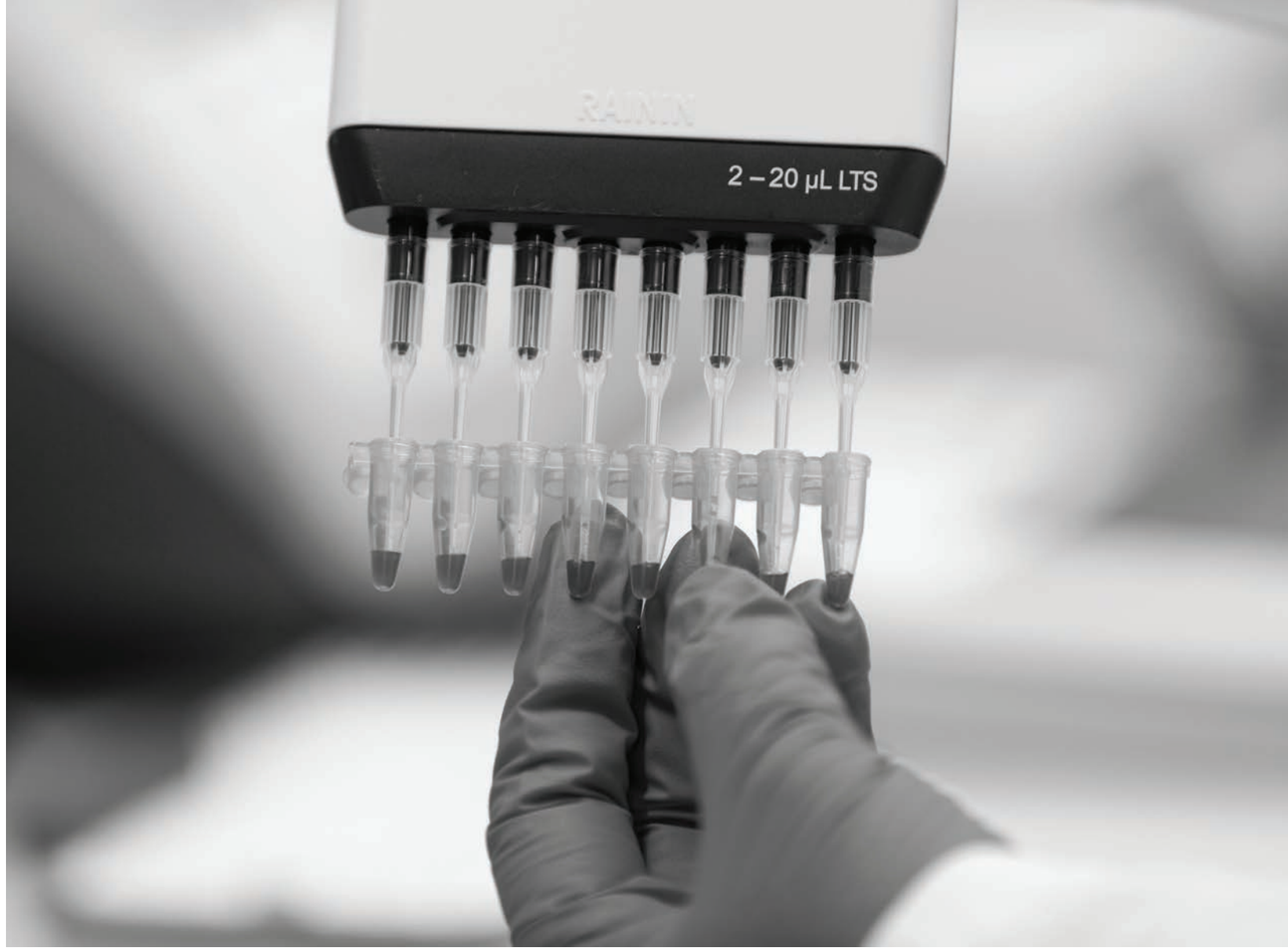
Genomics can be simply defined as the study of the genome, which is the instruction set encoded by the DNA inside of our cells and inherited from our parents. This DNA-based instruction set is interpreted during development as a carefully orchestrated process that builds cells, organs and ultimately an entire human body. Changes to the DNA code of an individual can result in disruptions of this process, resulting in altered development and human disease. The ability to rapidly discover and interpret these changes in individual patients across a variety of pediatric diseases has been accelerated in recent years by several factors.

First and foremost, complete sequencing of the first human genome (the Human Genome Project, 1990-2003) provided us with the fundamental instruction set in our DNA - namely the location and structure of the protein-coding genes that are shared by all members of the human population. Second, the advent of rapid and relatively inexpensive DNA sequencing technology, combined with advanced computational analysis has enabled genome sequencing to become a high-resolution form of diagnostic laboratory testing. Third, a series of "big science" efforts that catalyzed the study of thousands of individual human genome sequences and permitted the association of DNA-based changes within those genomes with many conditions including cancer, cardiovascular disease, autism and other behavioral disorders, epilepsy, craniofacial, cardiac, and other birth defects and various syndromic metabolic and developmental diseases.

Building upon these critical factors, the inclusion of genome-based diagnostics now enables comprehensive molecular testing for individual patients with complex and otherwise undiagnosed disease by evaluating the entire genome in an unbiased fashion to identify causative changes. This approach is in stark contrast to the single gene testing performed at most children's hospitals which often results in a very long diagnostic odyssey for the patients and their families.

Recognizing this potential of genomics to improve our understanding, diagnosis and treatment of childhood diseases, Nationwide Children's established the Steve and Cindy Rasmussen Institute for Genomic Medicine in 2016. The Institute represents a very unique fusion of capabilities including advanced genomics-centered research and development, clinical molecular diagnostic testing and high-performance analytical computing. The intersection of these capabilities enables our mission of interdisciplinary and collaborative research across multiple service lines with a goal of including genomics-based evidence as a critical component of medical practice. Achieving this mission has become manifest in a series of clinical translational protocols, each of which studies patients across a number of childhood disease phenotypes. For example, children who are diagnosed with a brain or other CNS tumor undergo comprehensive analysis of the genome in their cancer cells, in collaboration with our colleagues from Neuro-oncology, Neurosurgery, Pathology, Radiology and Radiation Oncology who directly care for these patients. The results of our analyses are discussed during a weekly tumor board attended by care providers from all of these specialties, with an aim to identify genomic features that may indicate new treatments or predict outcome. The same protocol has evaluated patients with sarcomas, with blood cancers of various types and more recently, with overgrowth syndromes that often are caused by mutations in cancer-related genes. In total, more than 230 patients have been studied on this protocol since January 2018 and over 93% of those studied had one or more medically meaningful results identified by our analyses.

Similarly, children with treatment-refractory epilepsy without a known inheritance pattern often undergo brain activity mapping and surgery to remove affected tissues and thereby eliminate or reduce the intensity and frequency of their seizures. Working with our colleagues in Neurosurgery, Neurology and Pathology, we have studied the genome from tissue removed at surgery to identify and characterize genomic changes associated with the cause of their disease. Many of these changes are unique to the affected



tissue and may reflect changes that emerged not from inheritance but instead from DNA copying errors during normal development and growth in utero. This protocol has evaluated over 40 patients to-date, with a return of medically relevant information in 35% of the patients studied. In most cases, this information will not impact patient care, but there is an intangible value in parents being able to understand the underlying cause of their child's seizures.

In collaboration with Nationwide Children's medical genetics providers, we annually study more than 300 children with undiagnosed syndromic or complex disorders thought to have underlying genetic causes. This test, which can be ordered through our clinical laboratory, evaluates the patient's protein coding genes in comparison to those of both parents, when possible, to identify changes unique to the child's genes that may provide clues to the disorder or help identify the syndrome. A clear determination of genetic cause is identified for around 33% of patients evaluated by this clinical test. In the event of a negative result, we may offer these families the option of enrollment onto our rare disease genomics protocol, which performs sequencing of the complete genomes of the patient and parents, and in some cases includes individuals from the family pedigree that are also affected. Using this comprehensive approach, we have uncovered complex changes to the DNA of affected individuals that explains their disorder or syndromic difficulties yet could not have been identified by the clinical test which only evaluates about 1.5% of the genome.

Our successes in the rare disease genomics protocol have led to a new effort that also focuses on whole genome sequencing of child and parents, but in this

case involves tiny newborns in our neonatal intensive care unit with a variety of failure-to-thrive related difficulties, including metabolic and developmental problems. The big difference in this procedure is our goal to return information about these babies to our neonatal ICU providers in only 48 hours! This time-to-results goal is a technical and logistical challenge that we are still tackling, yet we have already made significant progress, having returned information on our most recent case in only 4 days.

Two other areas of collaborative study have emerged in the past year. One area focuses on the relationship between our health and our microbiome, which is defined as the bacteria and viruses that naturally live in and on our bodies. Research has illustrated that this close relationship between humans and microbes shapes our illness and health in ways that had not previously been appreciated and has sparked further study in the pediatric realm. These studies include gaining a better understanding of the impact of vaccines and antibiotics on the normal gastrointestinal flora, adverse effects on normal flora caused by anti-anxiety medications and how microbes impact childhood neuronal development. Most recently we have opened a collaborative protocol with researchers and care providers in a new focus area at Nationwide Children's Behavioral Health. Here we will use the body of knowledge emerging from psychiatric genomics and autism genomics research to study pediatric patients and their families who have been diagnosed with autism, with depression leading to suicidality and with bipolar disorder. Long-term we anticipate our work in behavioral genomics will transition to the setting of genomic testing as a component of medical diagnosis for these children.

While strong progress has been made toward our mission at the Rasmussen Institute, it is clear that additional medical service lines will benefit from the integration of genomics into both research and clinical practice. To better identify and define these opportunities, a critical activity involves education of clinical providers regarding the application of genomics - what it can and cannot address. Similarly, we benefit from understanding the challenges and unanswered questions in these different areas of pediatric medical practice and using this information to shape study design, patient accrual and other important aspects that maximize the yield of information we obtain. With a basic understanding of each other's vocabulary, strengths and challenges, we can better define the way by which genomics can help answer the difficult questions that clinicians must address when diagnosing and treating their patients. This is the essence of team science in precision medicine and why genomics is an accelerator for our hospital and its important focus on providing the best care possible for our patients.

Genomics and Privacy

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Large scale data breaches are in the news frequently, hitting many different types of institutions, such as banks, corporate companies and even hospitals. In the digital age, it leads people to wonder about the security of their information and how data remains private. This is especially true in the world of genomics, where this sensitive data has a unique need to be shared for research, public health, clinical interpretation and medical practice support. As this information is shared for current and future research or treatment of genetic conditions, it is more valuable to cybercriminals than traditional protected health information (PHI) because of its ability to illuminate generational family health. The balance to keep it private and secure is paramount while at the same time remaining cognizant of the importance of sharing for advances in genomic research.

In the 1950s, cells were used from a cancer patient named Henrietta Lack and were utilized in multiple research projects.

It became known as the HeLa cell line. This was done without her or her family's consent, which was not uncommon at the time. When discovered, this led to discussions about consent, patient privacy, ethics, property rights and others. Those discussions continue today as the boundaries of privacy, patient understandings of consents, and precedence set on regulations or legal outcomes evolve. Informed consent is a large component of research and testing. This consent should be written, clear on the risks and benefits of participation and include whether data or specimens will be used for research. The research subject should have a good understanding of what the consent entails and have the opportunity to ask questions.

Privacy concerns with genomics impact not only the initial research subject, but also siblings, current or future children, and other family members. The institutional review board (IRB) and/or privacy board is designed to ensure maximum privacy protection while sharing the minimum amount of data, specimens, etc. Federal law requires adherence to these core procedures established by the Common Rule including the appropriate informed consent and the mandated review by the IRB.

Genomics data has the potential to impact denial of medical treatment, eligibility for healthcare insurance and qualifying for job opportunities. The Genetic Information Non-Discrimination Act (GINA) was developed to protect against discrimination in the workplace and healthcare insurance but there are still unprotected gaps, such as disability, life and long-term care insurance. GINA also does not apply to small employers and the U.S. military. The uncertainty and variability of what privacy protection is available can impact the participation of needed participants.

It is imperative that the privacy laws and regulations match the rapid pace of which science and the study of genomics evolve. Typically, deidentified data is absolved of federal and state privacy requirements but as technology advances, even the best deidentified data can be reidentified with accuracy. Future regulations will need to focus on addressing this to meet the needs of scientific advancements and privacy protection.

The Need for Speed: Rapid Genome Sequencing

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A rare disease is one that affects fewer than 200,000 Americans. However, because there are more than 7,000 rare diseases, they are collectively common, affecting more than 10% of all Americans. More than half of rare diseases have a genetic basis and disproportionately affect children. At Nationwide Children's Hospital, many children with rare genetic diseases are diagnosed and managed on an outpatient basis by providers in the Division of Genetic and Genomic Medicine. Historically, patients would undergo a series of genetic tests until a diagnosis was reached. The process was time consuming and frustrating for patients and families, often taking many years to reach a diagnosis. Within the Steve and Cindy Rasmussen Institute for Genomic Medicine at Nationwide Children's Hospital, exome sequencing has been available since 2017. Exome sequencing is a clinical test that allows the portions of our genes which code for protein to be studied for genetic variation which may be associated with disease. Exome sequencing has shortened this diagnostic odyssey for many patients from years to months or even weeks. However, for our sickest patients requiring intensive care, patients, families and doctors do not have the luxury of waiting even a few weeks for a diagnosis.

The current standard of care requires sending a sample to an external laboratory where results take up to two weeks.

Expediting a genetic diagnosis on a time scale that is relevant to critically ill children and their caregivers requires multiple service lines acting as one team. Investigators at the Steve and Cundy Rasmussen Institute for Genomic Medicine are partnering with clinicians in Genetic and Genomic Medicine, Neonatology, Critical Care and the Heart Center to understand how to deliver a genomic diagnosis in a timely manner and to study the impact this change in practice has on patients, families and clinicians. The process begins when the Clinical Genetics consult service is asked to evaluate an inpatient. When the primary service and the clinical geneticist agree that a rapid result may improve care, families are offered the standard of care as well the opportunity to enroll in an IGM translational protocol designed to rapidly sequence the patient's genome. Blood is drawn from the patient as well as both parents and sent to the lab for analysis. In parallel, the patient's clinical information is summarized and transmitted to the lab. Once DNA has been extracted, sequencing is completed in a process designed under the leadership of IGM co-investigator Dr. Vincent Magrini. This process generates a massive amount of data which needs to be accurately, but rapidly processed into a human interpretable form. Dr. Peter White, an Institute co-investigator, and his bioinformatics team have combined automation and cloud computing to enable rapid analysis. Once initial data are available, a collaborative team including researchers, variant scientists and analysts, genetic counselors and laboratory directors gather to review the results under the direction of Institute co-investigator Dr. Catherine Cottrell and Principal Investigator, Dr. Bimal Chaudhari. During this multidisciplinary review, data from the genome analysis are discussed to determine if any genetic variants are consistent with the patient's symptoms, or to reassure clinicians that certain suspected diagnoses are unlikely. In the first 6 months, the recruitment phase of the study, the team was able to reduce the time to provide a preliminary interpretation to under five days. While researchers have many additional investigations in mind, including using artificial intelligence to further speed up the process, the biggest impact on care will come when the test is transitioned out of the research setting and into clinical care.

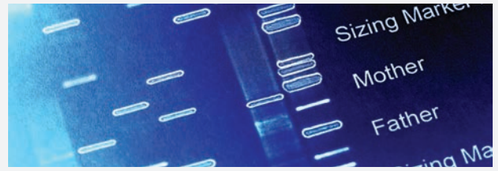
The translational nature of the rapid genome sequencing protocol was designed to enable an efficient transition toward offering genome analysis as a validated test within the Institute's Clinical Laboratory.

Because many steps within the translation protocol were thoughtfully laid out, including provider education, transport and handling of the specimens and data, as well as results analysis, the study team and laboratory personnel gained critical hands-on experience. The knowledge gained during the translational study allows for further refinement in the overall workflow, with the ultimate goal of providing a time-sensitive and comprehensive result for improved diagnosis and management in our most critically ill patients. Validation efforts in the clinical laboratory are thoroughly considered to ensure that a test is designed to be highly robust, accurate, and reproducible, while meeting necessary standards set forth by professional societies, and accreditation organizations. Once a test is clinically validated, the results can be directly shared with clinical providers to inform care, as well as documented in the patient's medical record. With researchers, clinicians, laboratory faculty and staff jointly focusing on best outcomes for our patients, the clinical realization of rapid genome sequencing at Nationwide Children's is soon to be a reality.

DEFINITIONS

The human genome *includes all coding and noncoding DNA sequences. DNA encodes more than 20,000 genes in humans, but most of the more than 3.2 billion base pairs that comprise the human genome are repetitive DNA or noncoding sequences and have not been linked to specific inherited disorders.*

Portions of our genes known as ***exons*** *encode the genetic instructions for making proteins which are fundamental components of our cellular makeup and biological functions.*



The human exome *includes all coding DNA sequences (exons). Comprising only 1%-2% of the human genome, the exome nonetheless contains the majority of currently recognized disease-causing variants in the genome.*

Exome sequencing *is a laboratory test designed to identify and analyze the sequence of all protein-coding nuclear genes in the genome. Approximately 95% of the exome can be sequenced with currently available techniques.*

Genome sequencing *is a laboratory test designed to identify and analyze the sequence of all coding and noncoding DNA.*

Sustaining Our Drive for 5!

Sherri Watts, MSN, RN, Professional Development

The American Nurses Credentialing Center (ANCC) Magnet Recognition Program® application criteria are revised every four years. Health care organizations apply Donabedian's structure + process = outcome framework to demonstrate the current state of nursing excellence.

Approximately 7% of all registered hospitals are bestowed Magnet® designation by the ANCC Commission on Magnet Recognition. A much smaller percentage of these hospitals have sustained Magnet designation for more than four consecutive journeys.

The current state of Nationwide Children's Hospital Magnet status is as an elite member of hospitals who are applying for a fifth consecutive ANCC Magnet recognition. Nationwide Children's is in year two of the four-year Drive for 5 themed Magnet Journey. The unprecedented times of virtual meetings, pivoting and welcoming several new hospital leaders has only strengthened our agile and innovative approach. Two employees new to their roles, Lee Ann Wallace MBA, BSN, RN, NEA-BC Senior VP Patient Care Services and Chief Nursing Officer and Vicki von Sadovszky, PhD, RN, FAAN, Director Professional Development have supported numerous innovative structures and processes to sustain our Magnet redesignation efforts.

Structure: One new structure is an automated potential Magnet story submission process available to all Nationwide Children's employees. Once vetted and assigned to a Magnet criterion, the Magnet Program Director and story author transition details, evidence and data into a Magnet Worksheet, followed by a Magnet Narrative Draft and final e-submission document. A second structure linked to employees submitting a potential Magnet story is the new Magnet Recognition Program. All employees who submit a potential Magnet story will receive a heartfelt Magnet Steering Committee Thank You. As soon as the story becomes a narrative draft, employees will receive a frameable Certificate of Completion highlighting the story and team. And finally, when the Magnet story is submitted into the final document, employees will receive an ANCC lapel pin.

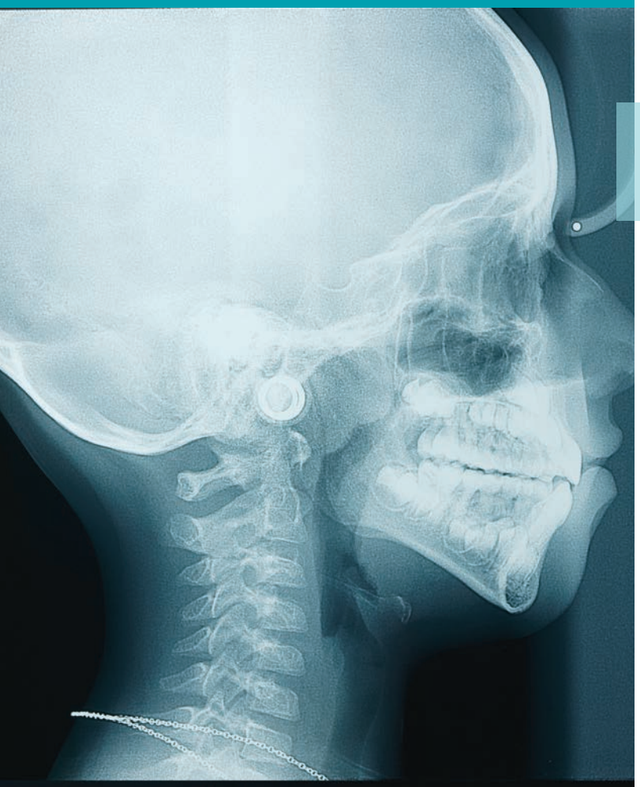
Process: A silver lining process recognized during the pandemic included endless digital workspace applications which facilitated continual acquisition of Magnet stories. Similarly acclaimed, was the training afforded by Vickie Bennett, DNP, RN-BC, who transitioned into a new role of eLearning Educator. Vickie and her team expanded use of virtual programs such as; IdeaBoardz, Adobe Spark, and Mentimeter. These new engagement platforms have become the foundation for brainstorming during virtual Magnet Story touch base meetings.

Outcomes: With 43 of the 82 required Magnet stories assigned, Nationwide Children's is well positioned for a successful fifth Magnet document. Our agile and innovative methodology to bumps along the road has made this journey one to cherish.

Precision Medicine and Next Generation Clinical Care in Pediatric Neuro-Oncology

Prajwal Rajappa, MD, MS

Assistant Professor of Pediatrics and Neurological Surgery Member, Translational Therapeutics Program, The James Comprehensive Cancer Center, The Ohio State University College of Medicine Director, Translational Neuro-Oncology Laboratory, Institute for Genomic Medicine



X-ray of a child's head, side view

From a policy standpoint, these new programs underscore a growing consensus among policy makers and government officials, industry and health care providers that molecular characterization of diseases could help identify clinically useful data.

In the United States alone, approximately 4,500 children are diagnosed each year with Central Nervous System (CNS) tumors.

Pediatric CNS tumors are classified as both malignant and non-malignant tumors of the brain and spinal cord.

There are two main types of CNS tumors: gliomas and medulloblastomas. Gliomas, tumors of glial origin, contribute to around half of all pediatric and adolescent CNS tumors, making them the most common CNS tumor in this population. There are two main types of gliomas: astrocytomas and ependymomas. Astrocytomas, tumors of astrocytes, are the most common type of glioma. Low-grade astrocytomas are classified into pilocytic astrocytoma (grade I), which are usually benign and diffuse astrocytoma (grade II). Low grade astrocytomas account for roughly 15% of all gliomas. High grade astrocytomas can be divided into anaplastic astrocytoma (grade III), diffuse intrinsic pontine gliomas (DIPG), and glioblastomas (GBMs, grade IV). Grade II astrocytomas exhibit better prognosis (median survival of six to eight years) compared to aggressive high grade GBM (median survival rate of 12 to 18 months). Ependymomas are tumors of ependymal cells, derived from primitive glia, that predominantly occurs in the brain. In addition to these, germ cell tumors, meningiomas and lymphomas of the brain demonstrate variability with regards to tumor and molecular heterogeneity. The disparate nature and histology of these tumors pose significant treatment challenges and variable outcomes.

These pose significant challenges for children diagnosed with multiple recurrent, high-grade, inoperable and infiltrative disease. The current standard of care for infiltrative disease consists of maximal safe resection followed by adjuvant therapy, including chemotherapy, radiation therapy or combination chemoradiation therapy, but these treatments are fraught with comorbidities and toxicities ranging from surgical complications, endocrine dysfunction, neurocognitive delay, and impaired neurologic function associated with multimodality therapies. Overall, current treatment approaches in this high-risk population has been problematic as demonstrated by poor five-year survival rates. These poor outcomes have served as a driving force and rationale to start expanding various multi-faceted approaches. These modern approaches now aim to leverage Next Generation Sequencing (NGS) technology and personalized medicine and take advantage of the precipitous fall in cost of using these platforms.

To that end, large scale genomic studies on a national scale have started to enhance our knowledge base as it pertains to the genomic and molecular characteristics of these disparate tumors. Programs such as the Precision Medicine Initiative (PMI), All of Us and the Cancer Moonshot have placed an emphasis and value in genomic profiling to better understand complex disease entities. These national programs have long and short-term goals. These short-term goals include building a knowledge base of genetics and cancer biology in order to enhance drug discovery while the long-term goals focus on bringing accessible precision medicine health care delivery to all areas of health care infrastructure. With the rollout of these programs, there is a drive for participants to provide biological samples, personal health information, and genetic information. This cohort of patients serves as a platform for researchers to understand disease process and mechanisms. From a policy standpoint, these new programs underscore a growing consensus among policy makers and government officials, industry and health care providers that molecular characterization of diseases could help identify clinically useful data. Despite a national emphasis and rationale for NGS integration into health care delivery systems, widespread genomics programs have yet to be incorporated in standard of care practice on the grass roots level. Additionally, we lack longitudinal data with regards to incorporating precision sequencing and its association to clinical management and outcomes.

At Nationwide Children's Hospital however, we are at the forefront of next generation clinical care in Pediatric Neuro-Oncology in our journey to best outcomes. Given the seamless integration of genomic medicine as an addition to the standard of care in our Pediatric Neuro-Oncology service, we are starting to appreciate the important implications of precision medicine and genomics-based approaches to complex disease entities. The Pediatric Neuro-Oncology Tumor Board engages in a weekly conversation with neuro-oncologists, neurosurgeons, radiation oncologists, neuropathologists, and genomics experts from Steve and Cindy Rasmussen Institute for Genomic Medicine at Nationwide Children's Hospital who all have one

goal in mind: to improve outcomes for our patients by integrating precision medicine approaches as an addition the standard of care. Led by world renown genomics experts Drs. Richard Wilson and Elaine Mardis, the Steve and Cindy Rasmussen Institute for Genomic Medicine. is at the forefront of genomic medicine and translation. From a programmatic standpoint, all patients with rare and refractory disease are nominated onto the Cancer protocol. Here tumor tissue and matching normal control blood samples may undergo germline analyses in addition to whole exome and RNA sequencing along with methylation profiling. The resulting data is reviewed in concert with the clinical course for each patient during each tumor board meeting. Of note, the sequencing results are returned in a timely fashion so the data can be incorporated into clinical decision making and this is just one aspect of our program at Nationwide Children's that is exemplary. Overall, this multi-disciplinary approach brings together a broad range of expertise to answer challenging clinical questions and design novel treatment strategies based on targeted therapies.

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There is value in also understanding that the overarching concept of precision medicine is evolving. While the initial emphasis has primarily focused on defining tumor intrinsic driver mutations, there is a growing body of data that suggests that the tumor microenvironment and extrinsic factors including infiltrating immune cells play a role in facilitating cancer progression. To that end, the growing field of immunogenomics within precision medicine is defining mechanisms by which innate and adaptive immune cells play a critical role in promote angiogenesis, invasion and chemotherapy resistance and treatment response. Furthermore, various studies in solid tumors have associated innate immune myeloid cells and tumor associated macrophages as indicators of poor prognosis in addition to their role in T-cell exhaustion which limits the adaptive immune system's ability to fight the tumor. Numerous studies and therapeutic strategies are now emerging to selectively deplete or reprogram myeloid cells in cancer. These cellular based strategies and tumor extrinsic approaches in addition to genomic medicine will define the next iteration of precision medicine. It is this next iteration that should also emphasize the critical need for longitudinal follow up of patient care that involved precision medicine along with tumor intrinsic and extrinsic approaches. We need to evaluate the association of precision medicine with clinical outcomes and appreciate the benefits in a more systematic fashion. For example, evaluating the standard of care approaches as a control arm in comparison to precision medicine protocols will serve as a method to evaluate outcomes with respect to utilized techniques. We must also continue to develop electronic medical record (EMR) capture tools in order to evaluate clinical parameters (radiographic and histologic) along with laboratory and basic research findings.

While the last few years have seen an increase in clinical sequencing studies in pediatric oncology, we still need to evaluate the impact longitudinally on patient care and outcomes. Various precision oncology basket trials also have shown preliminary progress but need further evaluation in refractory or relapsed cancers. Ultimately, a collective analysis of clinical and laboratory research data in conjunction with genomic findings will accelerate better opportunities for precision medicine in children diagnosed with cancer. Overall, our goal in the field of pediatric neuro-oncology is to improve the outcomes of these complex disease entities leveraging precision medicine so we leave a meaningful impact on patients and their families.

Pharmacogenetics and the Controversy on Medication Choices

Susan Colace, MD, MSCI Assistant Professor of Pediatrics Co-Director for the Program in Personalized Medicine and Pharmacogenomics Pediatric Hematology/Oncology/BMT

Most medications we use to treat childhood diseases are chosen based on a variety of factors: the type of disease, whether the patient has any allergies, whether the drug comes in liquid or tablet form, the experience of the health care provider with that medication and so on. Once the medication is chosen, we typically calculate a dose based on the child's weight and height and we may even adjust the dose by measuring drug levels. Usually, this time-tested method works well, and the chosen medicine works at the prescribed dose.

For some patients and some diseases, however, this process is far more challenging. Patients may try medication after medication, only to find that one medication has terrible side effects, and another doesn't work at all. Another patient may have multiple drug levels drawn over weeks and months, never quite able to find the dose that works for them. Patients, families and providers all end up frustrated and discouraged that a medication simply isn't working the way it is supposed to, and may start to wonder: is there a better way to do this?

Pharmacogenomics is the study of how our genes interact with medications, also known as drug-gene interactions. Our genes are like an instruction manual for our whole body. That includes instructions on how our bodies process medications. Some genes control how medications are absorbed, broken down and removed from the body, while others control how medications are moved around the body to the places they need to go. Small changes in these genes, called genetic variants, can cause two people to process the same medication very differently. They may be the same size, and have the same disease, but need very different doses or respond very differently because of differences in their genes.

We are constantly learning about drug-gene interactions and how they can be useful to patients. Currently, there are more than 375 unique drug-gene pairs in a database frequently updated by the Clinical Pharmacogenetics Implementation Consortium (CPIC). Not every drug-gene pair is actionable. An actionable drug-gene pair means that finding a genetic variant would change the way a provider prescribes the drug. Some drug-gene pairs are informative and simply give us a better of understanding of why two individuals might respond to the same drug in different ways. Some drugs do not have any known genetic variants that affect the way they are processed in the body. Therefore, not every patient will benefit from genetic testing for selection or dosing of medications. Genetic testing is beneficial for those who are going to be taking medications that have a known, actionable, drug-gene interaction.

One misconception regarding pharmacogenomic testing is that it will allow the provider to choose the best medication for the patient. Pharmacogenomic testing cannot identify an individual medication as the best choice for a patient. Rather, it identifies whether there are medications that a patient is less likely to respond to, more likely to have side effects from or more likely to have trouble finding the right dose.

The other challenge with pharmacogenomic testing is finding the right time to test for variants in genes that might affect medication choice or dosing. Most pharmacogenomic testing takes several weeks to get results. For patients who need to start a drug very quickly, it can be difficult to have results back in time to be useful. Once a patient has started a medication, pharmacogenomic testing is less useful, as the patient will have already experienced side effects or a need for dose adjustment. Therefore, the best time to perform pharmacogenomic testing is before a patient starts any medications for a particular disease or problem.

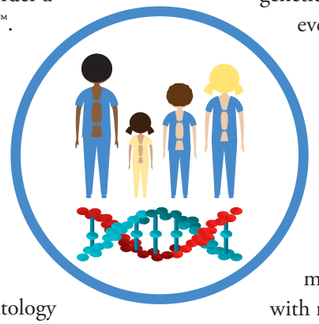
There are currently multiple commercial tests available that test for variants in a large number of pharmacogenes, some of which can even be ordered for testing at home, without a health care provider. While these can be interesting and sometimes helpful, most of these large panels test for variants which primarily affect drugs used in adults, and often the interpretation of the results is aimed at adults, rather than children. In some cases, the interpretation may lead a provider to avoid a medication which could be safely tried in a patient, thus unnecessarily eliminating a medication choice.

Every patient's situation is unique, and it can be helpful to discuss options for testing, as well as interpretation of test results with an expert in pharmacogenomics. Experts at Nationwide Children's Hospital can help determine whether pharmacogenomic testing would be helpful in a particular child's case or can assist in interpretation of pharmacogenomic testing results.

Genetic Counseling and Translational Medicine

Theresa Mihalic Mosher, MS, CGC, Licensed Genetic Counselor, The Steve and Cindy Rasmussen Institute for Genomic Medicine

Genetic counseling has been around since the 1970s, but the field has grown and become more visible to the public in recent years. However, what genetic counseling is and how it can be beneficial to patients and families continues to evolve over time. Genetic counseling is defined by the National Society of Genetic Counselors as "a process to evaluate and understand a family's risk of an inherited medical condition." In practice, this can mean many things. Genetic counselors are involved in a variety of settings, from hospitals and obstetric offices, to cancer centers and laboratories. You might even talk to one on the phone or by video chat if you order a direct-to-consumer test like 23andMe™.



At Nationwide Children's Hospital, genetic counselors wear many hats to serve our (primarily) pediatric population in very specific ways. We work all across the institution, in the general genetics clinic, Division of Genetic and Genomic Medicine, specialty sections like Cardiology, Neurology, Neuromuscular and Hematology and in the clinical laboratory. We are increasingly becoming involved in translational research with the Abigail Wexner Research Institute and the newly dedicated Steve and Cindy Rasmussen Institute for Genomic Medicine at Nationwide Children's Hospital. This allows for a true bench-to-bedside approach to genomic medicine, giving genetic counselors the ability to literally translate genomic research results and data into informative and actionable clinical information for patients. Some genetic counselors now hold dual roles, seeing patients in the clinic part-time and working on research projects the rest of the time, thus allowing for patients at Nationwide Children's to take full advantage of genomic testing available on their journey to diagnosis.

The goal of a genetic counseling session is never to tell people what to do with the genetic information, but to empower patients and families to take control of their medical decision making; giving them the information needed to help them decide whether or not genetic testing is right for their families. If they do undergo testing, genetic counselors coordinate and facilitate testing, and then explain what the results mean in the context of the family health history and patient's personal medical history. Whether positive or negative, genetic test results are complex, and helping individuals understand the relevant information can have implications for their health and decision making–treatments to use, treatments to avoid and what the risks to other family members might be. While genetic testing might not be the right path for everyone, many individuals and families are increasingly finding the results useful to them, not only for their personal health or the health of their child, but also for finding their own support community.

While genetic testing technology has improved exponentially over the years and people are able to be diagnosed more rapidly, there are still many patients with rare, undiagnosed diseases. Based on the National Institute of Health's definition of a rare disease, about one in 10 people in this country are affected by one. Despite the fact that about 80% of rare diseases are thought to be genetic, we don't yet know the genetic cause for all these diseases.

The Steven and Cindy Rasmussen Institute for Genomic Medicine is uniquely situated in the gap between diagnostic clinical testing and the world of genomic research. The Institute has created a model for translational genomic medicine that allows patients in the clinic with rare undiagnosed diseases who have reached the end of their clinical genetic testing road to be considered for newer types of diagnostic testing that have yet to be rolled out in the clinical arena. Patients who receive genomic sequencing or other types of genomic analyses on a research basis are helping to advance science. We are learning more about genes that have an unknown function in the body and describing new presentations of established genetic diseases. In about 30% of our rare disease research cases, patients are also receiving information that ultimately leads to a diagnosis via clinical genetic testing guided by research findings.

While knowing your genetic diagnosis doesn't always change your medical care, it does provide a name and an explanation for the condition. It allows family members who might be at risk to be more easily tested, and couples who are at risk to have child with the disease to better understand what their reproductive options are. In a world where patients can connect across the globe, finding a genetic diagnosis often provides the patients and families with the opportunity to find a community where they can meet and connect with others with the same condition. For many patients, finding these communities can be an important tool for coping with a rare disease. In the future, the research being done to diagnose rare diseases may help aid in the development of treatments and therapies, such as gene therapy, that up until now, has we've only dreamed of.

As a genetic counselor, it's my job to help guide patients and families on their journey to best outcomes as they navigate the world of genetic testing, and to help them find the most up to date information and support resources for a rare disease. With the translational testing model at the Institute, the ability of genetic counselors to provide patients and families with that information has greatly increased, and will continue to grow in the years to come as our technology and understanding of genomics increases even more.

Crisscross Applesauce: Our Journey to Genetic Answers

Kellynne Werner, Parent

"We have a problem over here!" Those were the words that followed the statements of congratulations from the nurses and doctors of the operating room when we delivered our first born, Collins Avery, via C-section six years ago. As many first-time parents are, we were both terrified and ecstatic when we conceived. It felt even more exciting for us, as early on in our marriage we had suffered a first trimester miscarriage. Heartbroken from the loss, our main focus became making it through this pregnancy and giving birth to a healthy baby.

About halfway through our pregnancy, we knew that it was anything but typical. Collins was breech, with her bottom down and her legs up. Some parents like to give their babies cute names like Bunny or Pea during the pregnancy process. We, however, affectionately referred to her as our fold in half baby. Not only did she keep to one position, she also made herself comfortable on my right side and rarely moved. This always made her easy for the doctors to find during examinations and gave the nurses and technicians a good laugh when it came time to check her heartbeat.

On the day of my C-section, there was never a thought for concern. Collins had simply made herself comfortable and was too stubborn to move. Though the C-section went smoothly and Collins came out screaming with all her might, it was quickly realized that Collins' fold in half position wasn't just for her comfort, it was due to her physical development. My husband said "her feet are up by her head!" I said "I'm sure they're fine. She's been in that position for five months." But I was wrong. Both of her knees were dislocated and her feet stayed right up by her head. Not believing it was permanent, we figured she had been in that position for so long her muscles just needed to relax. We even had a staff doctor tell us to "swaddle her legs down" until they relaxed. But by day three in the hospital, we knew that her legs would need more than time and gravity; she needed an orthopedic doctor.

Our family has a history with orthopedics, as most of my childhood was spent in some sort of brace. I had shoe braces for club feet, a back brace for scoliosis and underwent countless knee surgeries. Throughout the years, multiple members of my father's side of the family have been impacted by and carried on orthopedic issues. It wasn't until my mid-twenties and a visit to a podiatrist after a foot injury that I was told I had Nail-Patella Syndrome. The podiatrist made this diagnosis based on my family and medical history and my physical presentation. Because I had doubts about Nail-Patella Syndrome, I enlisted my mother's help in researching all available information about it. The pictures alone were shocking. Not only did the issues seem similar to the ones my family had, but the accompanying text served as support of this diagnosis. After all of these years, we had the answer to so many of the issues my father, his siblings and I have experienced. So, when Collins was born with orthopedic issues, we assumed that she too had Nail-Patella Syndrome.

It wasn't long after Collins was born that we had our first visit with Matthew Beran, MD, from the Orthopedics team at Nationwide Children's Hospital. We were quick to tell him our family history and the diagnosis I had been given some years before. During our initial appointment, Dr. Beran listened and validated our thoughts and suspicions, but mostly played and chatted with Collins while he examined her. He shared with us plans for future surgeries that would need to take place to correct Collins' legs. He also thought it best for us to work with the Genetics department for additional answers. So, that's what we did.

Not long after our visit with orthopedics, we met Annemarie Sommer MD from the Division of Genetics at Nationwide Children's which has since been renamed to the Division of Genetic and Genomic Medicine. Dr. Sommer was eager to hear our story and very interested in Collins' case. We told her everything we knew about my pregnancy, my family history and my previous diagnosis. She was fascinated to hear about how my diagnosis came about, the plans the Department of Orthopedics had for Collins and what she could do to help. She suggested we go a step further and have Collins tested for Nail-Patella Syndrome. It was a simple blood test and could be done during Collins' first leg correction surgery at six months old. Perfect! We had a plan.

After Collins' first leg surgery, we spent several weeks caring for her as she adjusted to her new leg— fit with cast accessory. We modified seats, toys and beds in order to increase her comfort. It was a learning process that we tried our best to master, as Collins was scheduled for a second operation in just a few weeks. It was around that time that we heard back from the Department of Genetics with some shocking news. Collins' test came back negative for Nail-Patella Syndrome. "How could this be?" we thought. The Genetics team explained that the testing for this particular syndrome was new and our Nail-Patella gene could still have a mutation that wasn't picked up by the test, or it could be a completely different condition. Though it wasn't the answer we wanted to hear, we knew that Nail-Patella Syndrome checked enough boxes to be a working diagnosis to utilize moving forward.

We are forever grateful for the opportunities the clinical genetics and research genomics teams provided to Collins and our family. Had it not been for their continued persistence to get the right answer, we would still be using our working diagnosis.

As the years passed, Collins quickly learned to navigate and adapt to her environment despite her abilities being slightly different than those of other kids. Both of her legs were corrected to give her a 90-degree bend, allowing her to walk and run. She seemed to run using her hips and waddle like a penguin when she walked. She worked with physical therapists to build quad strength, so she could climb stairs and use the equipment at the playground. Collins may have done things differently from other kids, but she continued to amaze us daily. We were consistently seen by the Departments of Orthopedics Genetics on a maintenance basis.

It wasn't until 2018 that we were contacted by the Rare Disease research team, genetic counselors, Theresa Mihalic Mosher, MS, CGC, and Erin Crist, MMSc, CGC, from the Institute for Genomic Medicine at Nationwide Children's, about the possibility of Collins being a part of a new genetics research study. This study was called "Genome Sequencing to Identify Causes of Rare Birth Defects and Birth Disorders." It would involve looking at the genes of multiple members of our family, including myself, my husband, my father and other extended family members who had orthopedic issues similar to Collins. The study was not a guaranteed answer to Collins' issues. It could take up to a year to hear back and there was a chance it would produce no further answers. Knowing we had Nail-Patella Syndrome as a working diagnosis that fit some of Collins' symptoms, we figured we had nothing to lose by participating and consented for the research study.

In the fall of 2018, we were contacted by Genetics with information that would forever change us. The research study had produced a result: a variant with Collins' FLNB gene. The same variant was also found in myself and my father. Shocked and surprised didn't even begin to describe the emotions we felt at that moment. An answer? A real answer to everything we have gone through? It almost seemed unreal.

Shortly thereafter, we met with Scott Hickey, MD, and genetic counselor, Betsy Schmalz, MS, LGC of the Genetics team at Nationwide Children's, where we learned that the FLNB gene is commonly linked to a known genetic condition called Larsen Syndrome. It is a congenital disorder associated with large joint dislocation that also affects connective tissue. They provided us with a multitude of information about it. The team also spoke with us about additional abnormalities it could include, and set up additional testing to rule out further complications. We were happy to later find out that Collins did not suffer from any of the rare abnormalities and her condition was primarily orthopedics related.

Today, Collins is a bright and bouncy 6-year-old. She continues to struggle with issues related to her knees and legs, but if you asked her, the only thing she can't do is sit crisscross applesauce. Though information about Larsen Syndrome is limited, Collins' medical team is now able to research and work with leading experts to get her the best care possible.

We are forever grateful for the opportunities the clinical genetics and research genomics teams provided to Collins and our family. Had it not been for their continued persistence to get the right answer, we would still be using our working diagnosis. Knowing that Collins has Larsen Syndrome allows us to plan for her future and the potential obstacles she may face.

Opportunity Out of Crisis: Telehealth Implementation in Response to COVID-19

Jennifer B. Reese, PsyD and **Ujjwal Ramtekkar, MD, MBA, MPE, DFAACAP,** Big Lots Behavioral Health Services

On the heels of increasing capacity by opening the Big Lots Behavioral Health Pavilion on March 10, 2020, a disturbing trend was noted: no show and cancellation rates were spiking in ambulatory care areas of the service line. Given the timing, it was reasonable to draw the conclusion that families were reluctant to attend their appointments at Nationwide Children's Hospital for fear of exposure to a virus that would soon take over nearly every moment of our waking reality. Rather than watching this continue to play out, Behavioral Health quickly mobilized to ensure continuity of care for the families we serve.

A group of clinical leaders within Behavioral Health quickly coalesced and made the pivotal decision to transition as many ambulatory services as possible to a telehealth model of delivery. Under ordinary circumstances, this was a project that would have taken at least a year to come to fruition. In these extraordinary times, it was accomplished in less than a week.

Never was One Team spirit or agility and innovation on fuller display. Patient Access Representatives were quickly equipped with a script and were soon working tirelessly contacting families to notify them that their behavioral health services would be delivered via telehealth for the foreseeable future. Families expressed a range of reactions, including trepidation, but the prevailing one was gratitude. Overwhelmingly, families were grateful that we were prioritizing their safety and had found a way to continue their care without increasing their risk of exposure to a virus that we continue to learn more about each day.

After rapidly developing a partnership with Information Services, telehealth functionality was ready for use within EPIC in record time. Educational materials were developed overnight, compiled, and sent out to our staff for review and completion. Among these was a workflow document outlining how the interventions implemented through the Zero Suicide initiative should be adapted to the telehealth format to help keep some of our highest risk patients safe.

Based on the most current data available, Behavioral Health is quickly approaching telehealth volume of 5,000 visits per week across all our ambulatory services (Behavioral Health Therapy, Psychiatry, Psychology). With each passing week, our staff get better accustomed to the technology and providing care in this format. With such a sudden increase in volume, there have been some valuable lessons learned that have persisted over time.

We were able to transition to a telehealth model of care so rapidly due to existing experience and expertise within our service line. Initiatives such as Project ECHO (Extension for Community Healthcare Outcomes) meant we were ahead of the curve in terms of interfacing with other professionals and families in a virtual manner. Additionally, a pre-existing partnership with the Telehealth Committee, which had been established approximately a year ago, allowed us to leverage foundational planning already in place. The lesson learned: never stop innovating.

One of the most substantial benefits of providing telehealth services is our office-based providers being able to observe the patient and their family members in their home environment. For example, we have been able to directly observe behavioral difficulties previously only described to us by caregivers, which also then allows us to provide real time coaching to the parent on behavior management interventions. This also has the added benefit of the family practicing these skills in the environment in which they will be utilized, which encourages generalization.

Care in this format also reduces barriers for some of our patient population. Traveling with unreliable transportation or to a clinic a long distance away are less stressful circumstances, and in some instances, no longer problems. Many of our families have multiple children, so not having to transport everyone to an office or arrange for childcare reduces stress and strain.

Challenges that have persisted over time are a subset of our families experiencing connectivity difficulties, low trust in technology or specific applications, and/or lack of confidence in using technology. This is further complicated by our current inability to provide in-person technology support. More specifically, we are asking families who are already frustrated, stressed, and experiencing challenges with technology to access support remotely. Further, unique challenges have been experienced by those families for whom English is not their first or primary language. Fortunately, our partners in Interpreter Services, Community Education and Information Services have been rapidly working to develop materials and resources for these families as well.

As we look ahead to the gradual reopening of our clinics, the natural question of how we continue to utilize what has proven itself to be a tremendous patient care asset has arisen. We look forward to further conversation with our leaders about how to strategically maintain this resource for our patients and their families.

In Recognition

In Recognition, a twice yearly feature in In Patient Care, recognizes clinical operations staff in their pursuit of education advancement and knowledge sharing.

Presentations

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Christensen C., Rosenberg N., Truba N. "Practical Approaches to Enhancing Compliance with Rehabilitation Recommendations Such as Bracing and Home Exercise Programs." American Academy of Cerebral Palsy and Developmental Medicine; September 2020.

Drake A. "Change Up: Clinical Considerations for Treatment of Softball Pitchers." "10th Annual Bodies in Motion: Unique Concepts for Upper Extremity Rehabilitation and Return to Sport in Youth Athletes; June 2020.

Findlen U. "When You Know Better, Do Better." American Academy of Audiology Annual Conference Pediatric Grand Rounds; April 2020.

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Kent M. "Fish Out of Water: Functional Considerations for Shoulder Rehab in Swimming Athletes." 10th Annual Bodies in Motion: Unique Concepts for Upper Extremity Rehabilitation and Return to Sport in Youth Athletes; June 2020.

Lazzara-Mould V. "TR at Nationwide Children's Hospital: Serving A Broad Population Effectively." The University of Toledo Summer Internship; July 2020.

Malloy K. "Mastering the Basics: UE Considerations for Returning to Tumbling in Gymnasts and Cheerleaders." 10th Annual Bodies in Motion: Unique Concepts for Upper Extremity Rehabilitation and Return to Sport in Youth Athletes; June 2020.

Matune J., Houpe T. "Return to School and Community Following a Pediatric Mental Health Hospitalization: A Therapeutic Recreation Approach." The American Therapeutic Recreation Association 2020 Virtual Conference Empowering RT Heroes; October 2020.

Matune J., Lazzara-Mould V. "TR, EBP, and Telehealth: How One Hospital Responded to the 'New Normal'." The American Therapeutic Recreation Association 2020 Virtual Conference Empowering RT Heroes; October 2020.

McKim M., Mount K. "Evidence-Based OT Practices to Support Return to School & Community Following Pediatric Psychiatric Hospitalization." American Occupational Therapy Association National Conference; April 2020.

O'Rourke S., Miller J., Sadler A. "Considerations for Re-Opening Pediatric Clinics in the Midst of a Pandemic." American Occupational Therapy Association Webinar Series; June 2020.

Puckett A. "Pediatric Voice Health Care from a Speech Pathology Viewpoint." World Voice Day Conference; April 2020.

Reifenberg G., Tanner K. "Administering Pediatric Assessments via Telehealth." Ohio Occupational Therapy Association; June 2020.

Rodriguez K. "The Way to Your Heart: Music Therapy with Cardiac Patients in a Pediatric Hospital." Great Lakes Regional Music Therapy Conference; March 2020; Schaumburg, Illinois.

Selhorst M., Selhorst B., Melfi N. "Treating the In-Season Youth Athlete." American Physical Therapy Association Combined Sections Meeting; June 2020.

Sheets S. "Keep Movin' in 2020: Clinical Implications and Practical Application of Rap/Hip-Hop in Music Therapy." Great Lakes Regional Music Therapy Conference; March 2020; Schaumburg, Illinois.

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Karnes J., Kennedy A., O'Keeffe C., Tennenbaum S. "Partnering with Parents to Provide Trauma-Informed Care Conference Simulation Education for Interprofessional Teams." IPFCC's 9th International Virtual Conference on Patient- and Family-Centered Care: Partnerships for Quality, Safety, and Equity; September 2020.

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Daisy Award

Danielle Aquila, RN

The quarterly Nationwide Children's Hospital Daisy Award was presented to Danielle Aquila, RN, of H5B. The Daisy Award is given in appreciation of the important difference our nurses make in the lives of our patients and families at Nationwide Children's.

Danielle received the Daisy Award for going above and beyond to make a patient and their family comfortable and confident during their stay.

Says Danielle's nominator, the parent of the patient: "My son was involved in a terrible accident. We were life flighted for injuries. On day three of our stay, my son woke up having a good morning, pain controlled, in good spirits, vital signs good. As the day went on the day changed he just wasn't the same boy as he was in the morning… Our nurse Danielle spoke up to say, 'He is just not the same boy, I think something is different.' The doctor listened and ordered an X-ray because of the belly pain and Danielle's assessment. A few tests later my child was in surgery! Surgery went well and he came back to his room and his belly pain was gone. He was on the road to recovery. If Danielle wasn't as attentive to us not only clinically but personally, we might not have the outcome we do! … Danielle is our super nurse and without her my child would not of had such an amazing recovery of body and soul!"

To learn more about our Daisy winners, and read their full nomination, visit **NationwideChildrens.org/Daisy-Award**

EVERYTHING MATTERS IN PATIENT CARE, previously published as *Heartbeat*, is a quarterly publication of the Patient Care Services Division of Nationwide Children's Hospital, Inc., Columbus, OH. Comments regarding the content of this publication are welcomed. References for articles are available by calling (614) 722 -5962. Articles may be reprinted with permission. Send all inquiries and material for publication to EVERYTHING MATTERS: IN PATIENT CARE in care of Joanna Kinner, Administration, Nationwide Children's Hospital, Inc., or call (614) 722-5962. Nationwide Children's Hospital is an affirmative action, equal opportunity employer.

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