2023 RESEARCH ANNUAL REPORT

Children's Hospital of Philadelphia®
RESEARCH INSTITUTE

Transforming Discoveries Into Solutions

Children's Hospital of Philadelphia Research Institute discovers, develops, and delivers solutions that change children's lives. In the 2023 Research Annual Report, learn how our work has a tangible impact as we accelerate research for clinical integration, create leading-edge technologies, and strengthen partnerships. Our unwavering commitment is to cultivate a world-class academic medical research community and spread our thought leadership worldwide to help children everywhere thrive.

CONTENTS

Bringing Our Science to the Bedside

CHOP clinical research laid the groundwork for U.S. Food and Drug Administration approvals of life-changing treatments, including three new therapies for rare diseases.

CHOP Research Paved Way for First FDA-approved Treatment for Friedreich's Ataxia

Slowing the Neurodegenerative Disorder

"As the first approved drug for FA, this is a major event not only for FA, but also for all ataxias and the rare disease community.

– David Lynch, MD, PhD

Children's Hospital of Philadelphia was a lead study site for the clinical trial that led to the approval of the first treatment for Friedreich's ataxia (FA) — an inherited neurodegenerative disorder that affects one in 50,000 people worldwide. Omaveloxolone (Skyclarys®, Biogen) is a once-a-day oral pill designed to improve neurological function and slow the progression of the disease.

"As the first approved drug for FA, this is a major event not only for FA but also for all ataxias and the rare disease community," said David Lynch, MD, PhD, director of the Friedreich's Ataxia Program, and an attending neurologist in the Division of Neurology at CHOP. "We are grateful for the support of the Friedreich's Ataxia Research Alliance (FARA), whose generous funding supported the background research that paved the way for this development, and to the patients who participated in the trials that led to this approval."

Dr. Lynch led studies showing that omaveloxolone — a potent activator of a transcription factor that regulates the cellular defense against oxidative stress — was shown to be effective at improving symptoms and slowing progression of the disease. The therapy sent patients "back in time," on average by a year or two, and kept them at that disease state for three to four years.

FDA Approves First Gene Therapy to Treat Duchenne Muscular Dystrophy

A Dose of Hope

"We're facing a tremendous foe, and for decades, scientists have been hammering away with various research attempts. Now we have what many of us believe is the first therapy that really is making a difference."

– John Brandsema, MD

The U.S. Food and Drug Administration's accelerated approval of the first gene therapy for Duchenne muscular dystrophy (DMD) was a major win for the field of gene therapy and for the one in 3,500 boys who are affected by the debilitating genetic disorder, according to Children's Hospital of Philadelphia experts. Most patients with the condition, which causes progressive muscle degeneration, do not live past young adulthood.

The drug, known as SRP-9001 (Elevidys®, Sarepta), is the 13th FDA-approved gene therapy. The approval was based on data from a small sub-group of patients, while a larger trial continues. CHOP, which houses one of the largest DMD treatment clinics in the country, is a participating research institution in Sarepta's ongoing, multinational Phase III clinical study to test the safety and efficacy of the drug. As part of the trial, two CHOP patients received a dose of the irreversible gene therapy.

While data from the large trial will not be available for several months, "time is of the essence for DMD patients and their families," said John Brandsema, MD, an attending neurologist at CHOP with expertise in treating children with neuromuscular disorders. For them, the fast-tracked approval of Elevidys offers a dose of hope.

"We're facing a tremendous foe, and for decades, scientists have been hammering away with various research attempts," Dr. Brandsema said. "Now we have what many of us believe is the first therapy that really is making a difference. It's not a cure, but we think these boys are potentially going to have many more functional years and a very different quality of life."

CHOP Leads Key Clinical Trial for Rare Cancer Treatment

A Milestone for Patients

"It is very exciting to have approval for frontline unresectable IMTs. This is an important milestone for these patients, and for pediatric oncology researchers ..."

– Yael Mossé, MD

Crizotinib (Xalkori®, Pfizer) — a first-generation anaplastic lymphoma kinase (ALK) inhibitor for patients with unresectable, recurrent, or refractory inflammatory ALK-positive myofibroblastic tumors (IMT) — received approval from the U.S. Food and Drug Administration.

Data from two multicenter clinical trials — one led by researchers at Children's Hospital of Philadelphia through the Children's Oncology Group (COG), which included 14 pediatric patients — and another trial that included seven adult patients supported the approval of crizotinib for IMT in July 2022.

Yael Mossé, MD, an attending physician at CHOP's Cancer Center and a professor of Pediatrics at the Perelman Medical Center at the University of Pennsylvania, has studied ALK alterations in the context of several cancers, including neuroblastoma. She was the principal investigator for the pediatric trial that led to crizotinib's FDA approval for anaplastic large cell lymphoma (ALCL) in January 2021, and now for IMT.

"The approval of Xalkori for ALK-positive IMT will bring hope to many pediatric patients and families who previously had highly limited treatment options," Dr. Mossé said. "It is very exciting to have approval for frontline unresectable IMTs. This is an important milestone for these patients, and for pediatric oncology researchers within COG and CHOP, who continue to seek out more rational therapies."

Hemostasis and Thrombosis Center Celebrates 50th Anniversary

From Home Infusions to Gene Therapy

"What started at CHOP as caring for 48 patients a year with hemophilia has grown into providing care for over 1,000 children with all types of bleeding and clotting disorders."

– Leslie Raffini, MD

The Hemostasis and Thrombosis Center (HTC) at Children's Hospital of Philadelphia celebrated 50 years of providing comprehensive care to children and adolescents with hemophilia and other inherited bleeding or clotting disorders. The Center was founded in 1973 as one of the first of its kind in the country. It is considered a Center of Excellence for the diagnosis, treatment, and prevention of bleeding and clotting disorders, serving as a national resource for other institutions.

"What started at CHOP as caring for 48 patients a year with hemophilia has grown into providing care for over 1,000 children with all types of bleeding and clotting disorders at our Center," said Center Director Leslie Raffini, MD. "It's been an incredible journey to witness the advancement of treatment options for our patients, which today includes an FDA-approved potentially curative gene therapy for patients with hemophilia B."

CHOP launched the Novel Therapeutics for Bleeding Disorders (NoT Bleeding) Frontier Program in 2023, which is housed in CHOP's HTC. This program will establish a national referral center for novel therapies in hemophilia and other rare bleeding disorders and develop novel therapeutic approaches, including drug repurposing, novel monoclonal antibodies, and gene therapies.

Virtual Diving Assessment Program Moves Research to Action

Developing Safe Drivers

"It's important that we ensure patients at CHOP learn how to be safe drivers so they can avoid involvement in crashes and the negative health consequences of crashes."

– Elizabeth Walshe, PhD

Children's Hospital of Philadelphia Care Network implemented a first-of-its-kind program that provides teens with a comprehensive evaluation of real-world driving skills in a safe, controlled environment. The program builds on a decade of research from the Center for Injury Research and Prevention and is supported by a gift from NJM Insurance Group.

Offered to adolescents during acute and well visits, the Virtual Driving Assessment (VDA) program identifies skills needed to be a safe driver and addresses the three most common serious crash risks: a lack of scanning needed to detect and respond to hazards, going too fast for road conditions, and being distracted by something inside or outside of the vehicle.

Once fully operational across the CHOP Care Network, researchers plan to measure the program's effect on licensing and crash data among young people in New Jersey and Pennsylvania.

"It's important that we ensure patients at CHOP learn how to be safe drivers so they can avoid involvement in crashes and the negative health consequences of crashes," said Elizabeth Walshe, PhD, a research scientist who investigates how cognitive development in young drivers may influence driver safety. "This study will help us identify teens at higher risk for crashes, based on their individual factors, and inform how we tailor driver training for these groups of teens."

Refining Tools, Techniques to Transform Pediatric Medicine

CHOP researchers and clinicians are developing novel technologies to make lifesaving predictions, treat patients, and advance clinical research.

Researchers Develop In Vivo Gene-Editing Model for Blood Disorders

Medicine of the Future

"The potential of this technology is transformative."

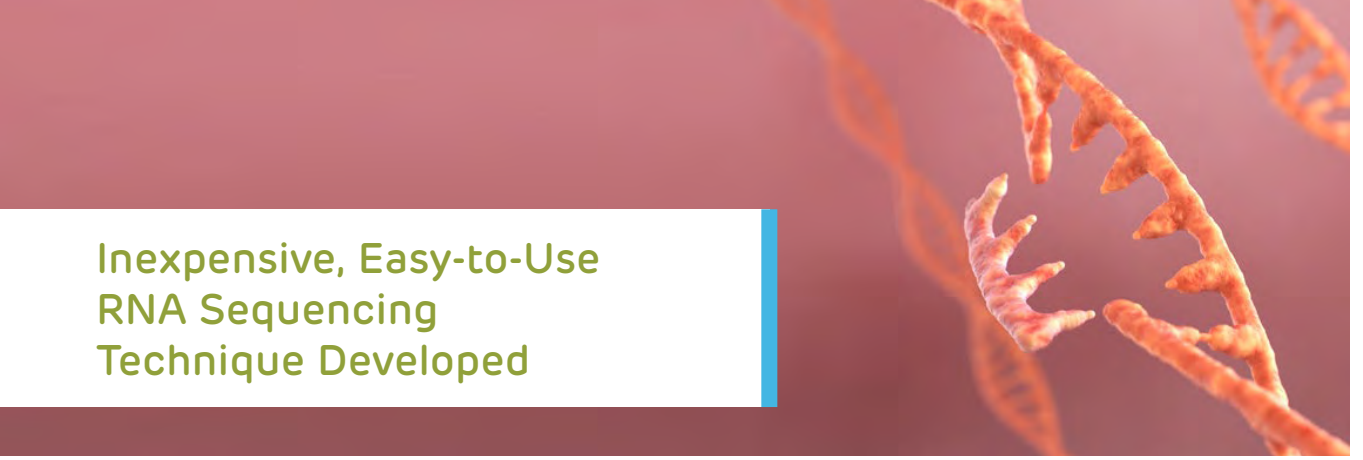
– Stefano Rivella, PhD

A team of Children's Hospital of Philadelphia and University of Pennsylvania investigators developed a proof-of-concept model for delivering gene-editing tools to the bone marrow. The approach, described in the journal *Science*, could expand access and reduce the cost of gene therapies for blood disorders.

"Right now, if you want to treat hematologic diseases like sickle cell disease and beta thalassemia with gene therapy, patients must receive conditioning treatments like chemotherapy to make space for the new, corrected blood cells, which is both expensive and comes with risks," said co-senior author Stefano Rivella, PhD, the Kwame Ohene-Frempong Chair in Pediatric Hematology at CHOP.

The researchers showed that it is possible to replace diseased blood cells with corrected ones directly within the body, eliminating the need for myeloablative conditioning treatments and streamlining the delivery of these potentially life-changing treatments.

"The potential of this technology is transformative," Dr. Rivella said. "In this paper, the technology is meant for bone marrow and red blood cell diseases. But this technology can potentially treat other diseases. If we could deliver a cargo that corrects a mutation in the bone marrow, we can conceive alternative formulations to correct mutation in the brain, lung, or liver — this is the technology that will allow us to do that."



Inexpensive, Easy-to-Use RNA Sequencing Technique Developed

A Tool for a Range of Disease

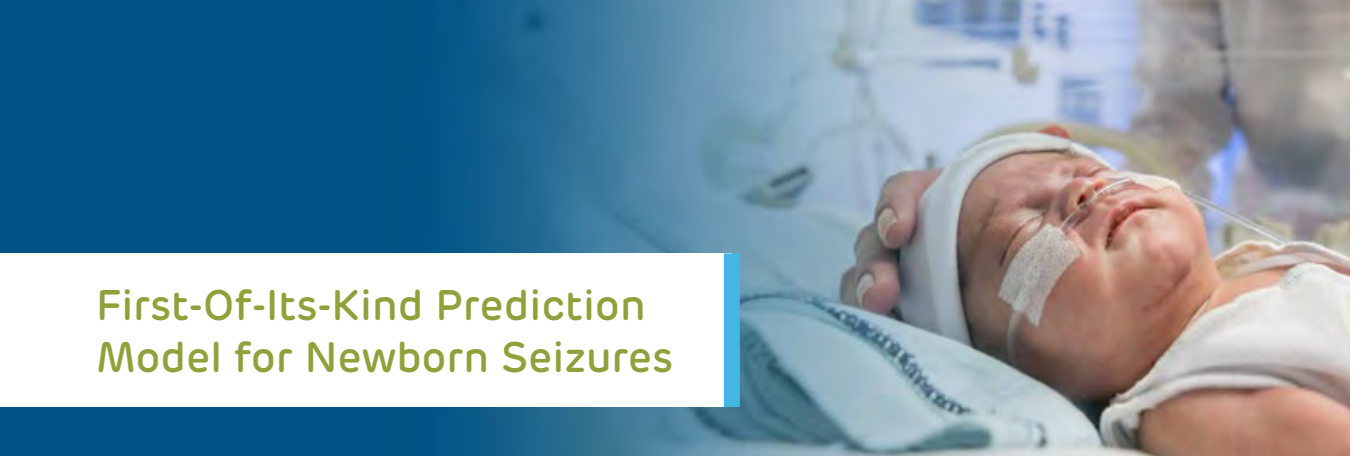
"This has the potential to accelerate discovery of new diagnostic and therapeutic solutions for a wide range of diseases."

– Lan Lin, PhD

In a development that could accelerate the discovery of new diagnostics and treatments for a wide range of diseases, researchers from Children's Hospital of Philadelphia developed a technology for targeted sequencing of full-length RNA molecules. The technology, called TEQUILA-seq, is cost-effective compared with other available methods for RNA sequencing and can be used for a variety of research and clinical purposes.

RNA sequencing is used to study how changes in RNA molecules can lead to diseases such as cancer. Current "long read" RNA sequencing platforms evaluate molecules that are more than 10,000 bases in length, but they are only modestly effective. Targeted sequencing, which involves enriching specific nucleic acid sequences before sequencing, is a way to overcome this, but can be expensive and complex to do.

"TEQUILA-seq solves that problem by being both inexpensive and easy to use," said Lan Lin, PhD, assistant professor of Pathology and Laboratory Medicine and a principle investigator in the Raymond G. Perelman Center for Cellular and Molecular Therapeutics. "The technology can be adapted by users for different purposes, and researchers can choose which genes they want to sequence and make the reagents for target capture in their own labs. This has the potential to accelerate discovery of new diagnostic and therapeutic solutions for a wide range of diseases."



First-Of-Its-Kind Prediction Model for Newborn Seizures

Avoiding Unnecessary Procedures

"This data helped us optimize which newborns should receive EEG monitoring in the NICU."

– Jillian McKee, MD, PhD

Using data from more than 1,000 newborns, researchers from the Neuroscience Center at Children's Hospital of Philadelphia have developed a prediction model that determines which newborn babies are likely to experience seizures in the Neonatal Intensive Care Unit (NICU).

This model could be incorporated into routine care to help the clinical team decide which babies will need electroencephalograms (EEGs) and which babies can be safely managed in the NICU without monitoring through EEGs.

"This data helped us optimize which newborns should receive EEG monitoring in the NICU," said first study author Jillian McKee, MD, PhD, a neurogeneticists and epileptologists provider with the Epilepsy Neurogenetics Initiative (ENGIN) Frontier Program at CHOP.

The researchers built their seizure prediction models based on standardized EEG features reported in electronic medical records. The retrospective study found that these models could predict seizures, and particularly seizures in newborns with temporary lack of oxygen to the brain, known as hypoxic-ischemic encephalopathy (HIE), with more than 90% accuracy. The models could be tuned to not miss seizures, performing with sensitivity of up to 97% in the overall cohort and 100% among newborns with HIE while maintaining high precision.

"If we can further validate this model, it could enable a more targeted use of limited EEG resources by reducing EEG use in low-risk patients, which will make care of babies with neurological concerns in the NICU more personalized and focused," said Ingo Helbig, MD, a pediatric neurologist in the Division of Neurology and co-director of ENGIN Frontier Program at CHOP. "We believe incorporating this model into real-time clinical practice could greatly improve the quality and efficiency of the care we deliver in these critical early days of life."

Researchers Study 'Peanut Patch' to Help Children With Food Allergies

A New Method for Young Toddlers

"It could be one more tool in an allergist's toolbox to help prevent a life-threatening allergic reaction."

– Terri Brown-Whitehorn, MD

Children's Hospital of Philadelphia researchers showed that exposing the skin to a small amount of peanuts desensitized a majority of peanut-allergic toddlers, in a Phase III clinical trial.

Approximately 2% of children in the United States, Canada, and other western countries experience peanut allergies. Peanut oral immunotherapy (OIT) can desensitize allergic children to peanuts by having them consume very small but increasing amounts of the allergen over time. However, OIT involves regular, demanding dosing schedules, side effects, as well as the risk of allergic reactions.

As an alternative, researchers have been investigating the use of epicutaneous immunotherapy (EPIT), which involves a patch containing a small amount of allergen that is placed on a child's back, exposing the immune system to a very low level of allergen with less risk of a systemic reaction.

After a year of treatment in this trial, a significantly larger percentage of those wearing the peanut patch were able to tolerate the required peanut dose – 67% of those wearing the interventional patch versus 33.5% of those wearing the placebo patch.

"Although an allergy patch won't necessarily work for all toddlers, this study shows that it could be one more tool in an allergist's toolbox to help prevent a life-threatening allergic reaction," said Terri Brown-Whitehorn, MD, an attending physician in the Division of Allergy and Immunology and co-leader of the Food Allergy Center Frontier Program. "If we can find ways to reprogram these children's immune systems, that's a step in the right direction."

Novel Technique to Analyze 53 Million Points of Clinical Data

The Power of Machine Learning

"The algorithm we developed in this study has the potential to be utilized in finding similarities between clinical trajectories and identifying novel genetic causes of diseases."

– Ingo Helbig, MD

Researchers from Children's Hospital of Philadelphia and Drexel University created an algorithm to analyze 53 million patient notes from more than 1.5 million individual patients to identify similarities in their medical histories that can help pinpoint potential risks for developing future diseases and the trajectory of those conditions.

This method of identifying phenotypic similarities exceeds the capacity of any other current computational models. The technique demonstrated a high degree of agreement with the judgment of experts in the various clinical fields represented in this data.

By analyzing data from 1,504,582 patients with a variety of diagnoses and syndromes with 53,955,360 electronic notes in the Arcus data repository, the researchers identified 9,477 distinct phenotypes. Arcus is a suite of tools and services developed at CHOP that links biological, clinical, research, and environmental data for the purpose of conducting innovative, data-driven research.

"The algorithm we developed in this study has the potential to be utilized in finding similarities between clinical trajectories and identifying novel genetic causes of diseases," said Ingo Helbig, MD, a pediatric neurologist in CHOP's Epilepsy Neurogenetics Initiative (ENGIN) Frontier Program and scientific director of the Arcus Omics program. "This will allow us to use machine learning in tandem with existing methods to analyze risks and patient prognoses in a more efficient manner at large scale."

Amplifying Our Impact and Expanding Opportunities

Funding from generous donors is propelling scientific and clinical research at CHOP.

Large Gift to Establishes Center for Epilepsy and Neurodevelopmental Disorders

Accelerating Collaborative Research

"This new center will fill the gap between the tremendous advances in early diagnosis and comprehensive clinical care."
– Madeline Bell

A $25 million gift from an anonymous donor to Children's Hospital of Philadelphia and Penn Medicine established the Center for Epilepsy and Neurodevelopmental Disorders (ENDD), accelerating collaborative research in genetic therapies for neurodevelopmental disorders. This gift will bolster the efforts of an interdisciplinary group of clinicians and scientists at CHOP and the Perelman School of Medicine at the University of Pennsylvania, led by director Benjamin Prosser, PhD and co-directors Beverly Davidson, PhD, and Ingo Helbig, MD.

ENDD will initially focus on developing therapies for disorders related to mutations of the STXBP1 and SYNGAP1 genes — which are linked to abnormal brain function, intellectual disability, epilepsy, and motor and behavioral impairments — with the goal of expanding its efforts to other genetic neurodevelopmental disorders over time.

"CHOP and Penn have systematically invested in integrated care programs for genetic epilepsies and neurodevelopmental disorders," said CHOP President and Chief Executive Officer Madeline Bell. "This new Center will fill the gap between the tremendous advances in early diagnosis and comprehensive clinical care and the development of new treatments for these patients."

‘Catalytic Funding’ Establishes the Topolewski Pediatric Heart Valve Center

After their daughter underwent multiple, life-saving surgeries at Children’s Hospital of Philadelphia during the first few weeks of her life, Ed and Kristin Topolewski felt compelled to give back. Their multimillion-dollar gift will further advance both clinical and basic science research at CHOP that is finding new solutions for children with complex heart valve diseases.

The funding has established the Topolewski Pediatric Heart Valve Center as well as the inaugural Topolewski Endowed Chair in Pediatric Cardiology, which is held by Matthew Jolley, MD, an attending physician in pediatric cardiac anesthesia and echocardiography.

Clearer Imaging, Better Interventions

“Having better models of these diseases and understanding the mechanisms that are leading to valve failure will have a profound impact on how we treat these patients.”

– Joseph Rossano, MD, MS

In addition to Dr. Jolley’s research, which uses 3D image-based computer modeling to inform surgical and interventional planning in children with heart abnormalities, the funding will help to support other projects, including minimally invasive techniques, innovations in imaging, and therapeutics.

“Heart valve abnormalities are very common in children, and yet, they can be some of the most challenging disorders to treat,” said Joseph Rossano, MD, MS, co-director of the Cardiac Center and chief of the Division of Cardiology at CHOP. “Having better models of these diseases and understanding the mechanisms that are leading to valve failure will have a profound impact on how we treat these patients.”

Gilbert Family Foundation Funding Accelerates Neurofibromatosis Type 1 Research

Harnessing CAR T cells

"Not only do we have the help of the NF1 patient community, but we have the knowledge, support, and infrastructure of the wider research community at CHOP and Penn, and I think that's really what makes us unique."

– Thomas De Raedt, PhD

Affecting one in every 3,000 people, neurofibromatosis type 1 (NF1) is one of the most common cancer predisposition syndromes that you've likely never heard of.

This year, the Gilbert Family Foundation established by Dan and Jennifer Gilbert, committed $5 million to fund three new CHOP projects focused on understanding the biology and discovery of new immunotherapy targets for brain tumors associated with NF1. The projects will be led by Chelsea Kotch, MD, MSCE, a pediatric neuro-oncologist; John Maris, MD, a pediatric oncologist and Giulio D'Angio Chair in Neuroblastoma Research; and Thomas De Raedt, PhD, a research scientist.

Dr. Kotch's projects will focus on gathering large-scale, quality data on patients with NF1 to establish standard-of-care guidelines and to inform further epidemiological studies. The project led by Dr. Maris and Dr. De Raedt will identify unique peptides in NF1 tumors that the research team can potentially target with CAR T-cell therapy.

"Not only do we have the help of the NF1 patient community, but we have the knowledge, support, and infrastructure of the wider research community at CHOP and Penn," Dr. De Raedt said, "and I think that's really what makes us unique."

Gates Foundation Funds COVID-19 Research at CHOP

Solving a Mitochondrial Mystery

"We hope to not only determine the importance of mtDNA variation in COVID-19 severity, but also to identify new approaches for mitigating the adverse impact of COVID-19."

– Douglas Wallace, PhD

Children's Hospital of Philadelphia received its first grant from the Bill & Melinda Gates Foundation this year. The multimillion-dollar funding will propel critical mitochondrial research to answer the question: Could genes of the DNA within the mitochondria, called mtDNA, lead to more severe symptoms associated with SARS-CoV-2 infection than others?

Since the beginning of the pandemic, researchers from CHOP's Center for Mitochondrial and Epigenomic Medicine (CMEM) and the COVID-19 International Research Team (COV-IRT) have demonstrated that SARS-CoV-2 has a striking adverse effect on patients' mitochondrial function.

Armed with this information, CMEM investigators will now determine if different mtDNAs affect individual sensitivity to COVID-19 by using cell lines they've developed that represent most of the major mtDNA lineages from around the world, as well as mouse models.

"With this transformative grant from the Gates Foundation, we hope to not only determine the importance of mtDNA variation in COVID-19 severity, but also to identify new approaches for mitigating the adverse impact of COVID-19," said Douglas Wallace, PhD, director of CMEM.

Cultivating a World-class Academic Medical Research Community

A commitment to innovation and inclusivity radiates with the launch of new programs, buildings, and centers.

First Arcus Omics Data Launch Enables CHOP Researchers to Jumpstart Their Research

Data Under One Umbrella

"A unique aspect of Arcus is that it can act as the honest broker on behalf of our researchers to collect and provide access to de-identified data, particularly the continuous update of rich clinical data that can be linked to genomic data."

– Ingo Helbig, MD

Children's Hospital of Philadelphia Research Institute and Arcus, CHOP's centralized research data repository, launched its first genomic dataset that includes more than 5,000 exomes and genomes and 12,000 chromosomal SNP arrays this year. The availability of this data will allow CHOP investigators to perform large-scale research while protecting patients' privacy.

Easy, hassle-free access to data is important for researchers to complete their work. This is particularly relevant in the genomics sphere where there is strength in numbers; however, genomic data is so sensitive that sharing it is not straightforward. To overcome this challenge, Arcus built a system within CHOP to make its institutional data available for researchers while providing a state-of-the-art privacy framework.

"A unique aspect of Arcus is that it can act as the honest broker on behalf of our researchers to collect and provide access to de-identified data, particularly the continuous update of rich clinical data that can be linked to genomic data," said Ingo Helbig, MD, scientific director of the Arcus Omics Team.

Breaking Ground for Breakthroughs With New Research Building

Building a Better Future

"It will make it easier for our teams to collaborate on the bench-to-bedside strategy CHOP is known for."

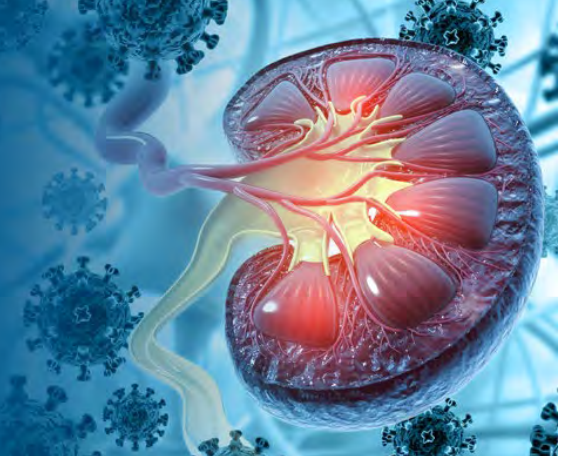
– Doug Hock

The skyline alongside Philadelphia's Schuylkill River will look a little different come 2025, as developers broke ground on the Schuylkill Avenue Research Building. Standing at 14 stories with 350,000-square feet of space, this state-of-the-art research facility will continue Children's Hospital of Philadelphia's century-long commitment to advancing children's health through innovative research.

"This building is an important part of our strategy to advance research at CHOP," said Doug Hock, CHOP Executive Vice President and Chief Operating Officer, at the groundbreaking ceremony. "It will make it easier for our teams to collaborate on the bench-to-bedside strategy CHOP is known for. It will help us attract and retain the very best scientists. It will make it possible to translate their discoveries into new treatments to change children's lives."

The international architecture firm Cannon Design created the Schuylkill Avenue Research Building's overall layout to encourage all the components of successful scientific discovery: collaboration, flexibility, and a dynamic nature. Wet labs, where scientists conduct biochemical and molecular studies, will be situated next to dry labs, where researchers analyze data sets, create computational tools, and develop new hypotheses for wet lab studies. The developers anticipate such a layout will stimulate a more seamless exchange of ideas and communication between researchers.

Penn-CHOP Kidney Innovation Center Celebrates its First Anniversary



Dual Strengths

"The center's ultimate vision is to provide an organizational framework that harnesses the unique strengths of CHOP and Penn to create an integrated clinical care and research model that will benefit patients with kidney disease across their life course."

– Michelle Denburg, MD, MSCE.

Children's Hospital of Philadelphia and Perelman School of Medicine at the University of Pennsylvania jointly launched the Penn-CHOP Kidney Innovation Center, in an effort to improve the lives of children and adults with kidney disease. During its first year, the Center hosted its inaugural symposium, recruited two new faculty members, hosted an international meeting, and launched its monthly seminar series.

The Kidney Innovation Center brings together scientists from across disciplines to focus on three main areas: fostering cutting-edge discoveries through collaboration between CHOP and Penn; recruiting and growing top talent to key areas that align with the Center's mission; and building the next generation of nephrology researchers through an enhanced training and mentorship program.

"We started with the symposium with the goal of bringing together people from many different fields, and that was quite successful," said Michelle Denburg, MD, MSCE, director of research for the Division of Nephrology at CHOP and an associate professor of Pediatrics and Epidemiology at Penn. She leads the Kidney Innovation Center with Penn's Katalin Susztak, MD, PhD, a professor of Nephrology and Genetics. "The Center's ultimate vision is to provide an organizational framework that harnesses the unique strengths of CHOP and Penn to create an integrated clinical care and research model that will benefit patients with kidney disease across their life course."

Following the success of the symposium, the Center's momentum continued with the Penn-CHOP Kidney Innovation Center's Seminar Series, which features monthly research in progress by postdocs, fellows, and faculty within the Penn-CHOP community. In May 2023, CHOP and Penn also hosted the biennial International Podocyte Meeting, bringing more than 400 scientists and clinicians from around the world together in Philadelphia. The formation of the Center also allowed CHOP and Penn to create a combined pediatric-adult fellowship in nephrology.

Bridge to Faculty Program Forges a Path to Academia for Underrepresented Scientists

Tools for Success

"The program not only focuses on scholars getting positions, but simultaneously provides them with the tools needed for success as they launch their independent academic careers."

– Paulette McRae, PhD

Children's Hospital of Philadelphia selected its inaugural pair of scientists to participate in the Research Institute's Bridge to Faculty Program.

Its goal is to prepare trainees from historically underrepresented groups for tenure-track faculty positions. Similar to the mentored phase of the National Institutes of Health's Pathway to Independence Award, the Bridge to Faculty Program provides a competitive salary, research training, and professional development that will put postdoctoral fellows on the competitive and rigorous path to professorship.

"This is a unique training experience designed to prepare exceptional senior-level trainees to be competitive in the tenure-track job market," said Paulette McRae, PhD, associate director of Specialty Programs and Diversity in the Office of Academic Training and Outreach Programs at CHOP's Research Institute. "The program not only focuses on scholars getting positions, but simultaneously provides them with the tools needed for success as they launch their independent academic careers."

Bridge to Faculty Program participant Amaliris (Ama) Guerra, PhD, is investigating how to fine-tune the immune system to deliver iron in a way that will safely increase red blood cell production in patients with thalassemia, who are at risk of iron overload. Another participant Zila Martinez-Lozada, PhD, researches the communication of cells in the brain using a combination of cell culture microscopy and transcriptomics, a technique used to study a cell's RNA molecules.

"I'm the product of all of these Philadelphia programs intended to create opportunity for people like me and to diversify academia. That has weight," Dr. Guerra said. "Now I get the opportunity to do science as a real job, which is something that doesn't exist for a lot of people."

New Frontier Program Aims to Deliver Novel Therapies for Inborn Errors of Metabolism

Improving Care While Making New Discoveries

"We are so excited to move the transformative new therapies being developed at CHOP and Penn into the clinic in order to improve the quality of life for our patients."

– Rebecca Ahrens-Nicklas, MD, PhD

Inborn errors of metabolism (IEM) are rare genetic disorders resulting in deficiency of key metabolic enzymes and can lead to serious complications if not treated or managed properly. Patients with inborn errors require close medical follow-ups, and most diagnoses are also associated with repeated hospitalizations.

The Gene Therapy for Inherited Metabolic Disorders (GTIMD) Program is a new Children's Hospital of Philadelphia Frontier Program announced this year to improve outcomes for these patients by creating a nationally renowned center dedicated to translating new molecular therapies from bench-to-bedside.

For the first time, curative molecular therapies are on the horizon for IEMs; however, for any treatment to be successful, it must be given early in the disease course, and patients must receive high quality subspecialist care for their many comorbidities.

Over the next three years, the GTIMD Frontier Program team — led by Rebecca Ahrens-Nicklas, MD, PhD; Can Ficicioglu, MD, PhD; and Sanmati Cuddapah, MD, all members of the Division of Human Genetics — aims to develop an innovative clinical program dedicated to the longitudinal care of IEM patients treated with molecular therapies. Additionally, they aim to translate novel molecular therapies developed at CHOP and the University of Pennsylvania into first-in-human clinical trials for IEM.

"We are so excited to move the transformative new therapies being developed at CHOP and Penn into the clinic in order to improve the quality of life for our patients," Dr. Ahrens-Nicklas said.

Disseminating and Implementing Research-informed Best Practices

CHOP is making a global impact with its research, contributing to new international concussion recommendations, standardizing neonatal resuscitation guidelines, and more.

CHOP Research Plays Major Role in New International Concussion Guidelines

Becoming Standard of Care

"Our ultimate goal is for visio-vestibular testing to be routinely performed on every child who may have a concussion."

– Daniel Corwin, MD, MSCE

An international panel of more than 100 researchers and clinicians released new scientific evidence and revised recommendations this year on the diagnosis, management, and prevention of concussions. Included in those recommendations is the visio-vestibular exam (VVE) — a clinical diagnostic tool developed and refined over the past decade by researchers and clinicians in Children's Hospital of Philadelphia Minds Matter Concussion Program.

The newest international recommendations on concussion are based on outcomes from the Sixth International Conference on Concussion in Sport, held in Amsterdam in October 2022, and published in the *British Journal of Sports Medicine* in June 2023. As part of the consensus statement released at the conference, the international group of experts recommended multiple assessment tools, including the new Child Sport Concussion Office Assessment Tool 6 (Child SCOAT-6). The VVE was incorporated as a key element of the Child SCOAT-6.

"Our ultimate goal is for visio-vestibular testing to be routinely performed on every child who may have a concussion," said Daniel Corwin, MD, MSCE, the Emergency Department lead of the Minds Matter Concussion Program, "regardless of where, when, and by whom their assessment occurs. The fact that the VVE has been recognized internationally as a critical evaluation tool for pediatric concussion is a significant step toward achieving that goal."

New Guidelines for Neonatal Resuscitation Studies Developed

Standardizing Research to Improve Outcomes

"We hope the Neonatal Utstein reporting guidelines will assist investigators engaged in neonatal resuscitation research and facilitate data pooling in meta-analyses, enhancing the strength of neonatal resuscitation treatment recommendations and subsequent guidelines."

– Elizabeth Foglia, MD, MA, MSCE

Researchers at Children's Hospital of Philadelphia led an international group of experts in developing new guidelines for neonatal resuscitation research. The guidelines were developed by the International Liaison Committee on Resuscitation Neonatal Life Support Task Force and published in the journal *Pediatrics*. They will standardize data definitions for those engaged in this area of research, allowing for better comparisons across studies and ultimately better outcomes.

Clinical research on neonatal resuscitation has accelerated over recent decades, but there are no standardized definitions or reporting guidelines for neonatal resuscitation clinical studies, making it difficult to compare studies or make clinical recommendations. To address this, the International Liaison Committee on Resuscitation Neonatal Life Support Task Force established a working group to develop reporting guidelines for neonatal resuscitation, based on similar guidelines that were developed for adults in 1990 in Utstein Abbey, Norway.

"We hope the Neonatal Utstein reporting guidelines will assist investigators engaged in neonatal resuscitation research and facilitate data pooling in meta-analyses, enhancing the strength of neonatal resuscitation treatment recommendations and subsequent guidelines," said first author Elizabeth Foglia, MD, MA, MSCE, an attending neonatologist with the Division of Neonatology at CHOP.

Development of First Diagnosis Guidelines for MOGAD

A Central Nervous System Disorder

"Consensus diagnostic criteria will allow us to conduct more robust clinical trials to investigate potentially superior therapeutic interventions and ultimately improve long-term outcomes for these patients."

– Brenda Banwell, MD

An international panel led by a Children's Hospital of Philadelphia expert established new criteria for properly diagnosing myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). The proposed guidelines are the first clinical guidelines for MOGAD and provide an important framework for distinguishing MOGAD from other neurological disorders.

MOGAD is a neurological disorder that causes inflammation and potential damage of the brain, spinal cord, and optic nerves. It can cause a wide range of symptoms, from vision loss and reduced color vision to weakness in the limbs, confusion, drowsiness, encephalopathy, and seizures. Without international consensus criteria about the disease, many MOGAD patients go undiagnosed.

"We hope that better and earlier diagnosis can lead to more patients receiving appropriate treatments," said Brenda Banwell, MD, co-director of the Neuroscience Center at CHOP and first author of the guidelines. "Consensus diagnostic criteria will allow us to conduct more robust clinical trials to investigate potentially superior therapeutic interventions and ultimately improve long-term outcomes for these patients."

CHOP Selected for New Program to Implement Cutting-edge Medical Evidence

Transforming Approaches

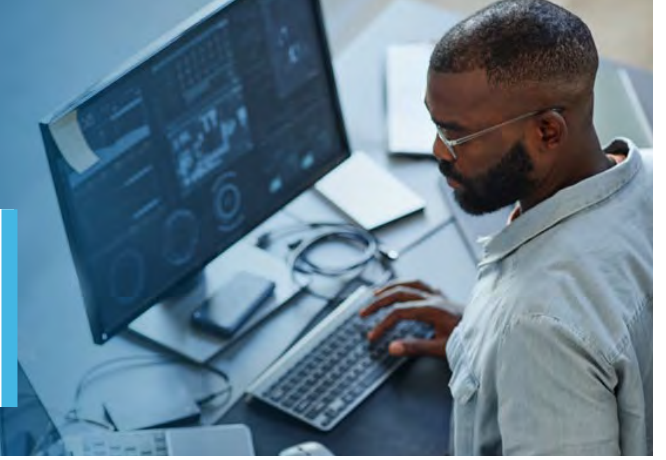
"This new initiative builds on prior successes we have achieved with PCORI funding in the area of antimicrobial stewardship, as well as ongoing work in the treatment of kidney stones and rheumatologic conditions in pediatric patients."

– Alexander Fiks, MD, MSCE

The Patient-Centered Outcomes Research Institute (PCORI) selected Children's Hospital of Philadelphia to participate in a new funding opportunity to promote the uptake of useful research results into practice.

The funding initiative, called the Health Systems Implementation Initiative (HSII), will provide funding to 42 participating healthcare delivery systems. At CHOP, this work will be led by Clinical Futures, a CHOP Research Institute Center of Emphasis, in partnership with the Center for Healthcare Quality and Analytics (CHQA).

"A main focus of Clinical Futures is in translating the best medical evidence into practice. The PCORI Health Systems Implementation Initiative will provide support to realize this goal for the benefit of patients and families," said Alexander Fiks, MD, MSCE, director of Clinical Futures and project lead for CHOP's participation in HSII. "This new initiative builds on prior successes we have achieved with PCORI funding in the area of antimicrobial stewardship, as well as ongoing work in the treatment of kidney stones and rheumatologic conditions in pediatric patients."



CHOP Researchers Create Open-Source Platform for Pediatric Brain Tumors

Sharing Discoveries

"We designed OpenPBTA so that anyone could access the data, contribute to its analysis, and/or use it in their own research."

– Jo Lynne Rokita, PhD

Researchers from Children's Hospital of Philadelphia, the Alex's Lemonade Stand Foundation Childhood Cancer Data Lab, the Children's Brain Tumor Network (CBTN), the Pacific Pediatric Neuro-Oncology Consortium (PNOC), and more than 20 additional institutions have partnered to create a first-of-its-kind open-source, reproducible analysis platform for pediatric brain tumors.

With the help of thousands of genomically sequenced samples, researchers used this platform to identify initial findings about genetic variants associated with poorer outcomes that could help guide future diagnostic and therapeutic advances. The details of the platform, called OpenPBTA, were published this year in the journal *Cell Genomics*.

"While there have been many proponents of an open-source model for scientific research, nothing like this existed for pediatric cancer," said Jo Lynne Rokita, PhD, a supervisory bioinformatics scientist leading OpenPBTA at the Center for Data-Driven Discovery in Biomedicine at CHOP and one of the study's authors. "We designed OpenPBTA so that anyone could access the data, contribute to its analysis, and/or use it in their own research."

Anna's Story: A Patient's Role in Furthering Friedreich's Ataxia Research

Read one research participant's story and the path to approval for the first drug to treat Friedreich's ataxia, a rare neurodegenerative disorder.

Anna's Story

Kristin Morrow first noticed an issue with her daughter Anna's balance during field hockey practice in 2015. Anna, who was 9 years old at the time and is now 18, had always been a natural athlete, so it struck Kristin that her daughter was struggling to get through a basic warm-up drill without tripping. In the weeks that followed, Kristin saw that Anna was stumbling during walks to school.

Anna Morrow, 18, was diagnosed with Friedreich's ataxia in 2015 and has received care at CHOP ever since.

"This was a kid who rode a bike at age 4," Kristin said. "She was very physically able, and I started to notice her regressing."

Following a visit with a pediatric neurologist and undergoing confirmatory genetic testing, Anna received a distressing diagnosis: Friedreich's ataxia (FA), a rare neurodegenerative disease that causes progressive damage to the nervous system. Symptoms typically begin in adolescence and worsen throughout a patient's lifetime.

Soon after Anna's diagnosis, a family friend recommended the Friedreich's Ataxia Program at Children's Hospital of Philadelphia, which was two hours from the family's home in Baltimore. Led by David Lynch, MD, PhD, the program is the largest of its kind in the world, providing diagnostic testing and lifelong disease management for patients.

The program is part of CHOP's Friedreich's Ataxia Center of Excellence, a collaboration of leading experts committed to promoting FA research and clinical care. FA research at CHOP has led to a greater understanding of the metabolic dysfunction underlying FA, the creation of an FA patient database, and the identification of more than 20 drug candidates that represent potential new therapies.

Since her first visit with Dr. Lynch in 2015, Anna has received care at the Center and, as a study participant, played a pivotal role in the search for FA treatment.

In the winter of 2023, Anna's family received potentially life-changing news: The U.S. Food and Drug Administration approved omaveloxolone (Skyclarys™, Reata Pharmaceuticals), the first treatment for FA. (Anna did not participate in the omaveloxolone trial.)


David Lynch, MD, PhD

The approval follows more than a decade of research led by Dr. Lynch and colleagues. Now, Anna and other adolescents like her around the country have access to a once-a-day oral pill that can slow the progression of the debilitating disease.

"These are individuals in high school and college who are losing the ability to walk, which makes those years of life much tougher," Dr. Lynch said. "Even forestalling that disease progression by a few years could be crucial to their development."

Navigating the Long Road to Drug Approval

FA affects the spinal cord, peripheral nerves, and the brain, resulting in uncoordinated muscle movement, poor balance, difficulty walking, changes in speech and swallowing, and a shortened lifespan. More than 95% of patients are wheelchair-bound by the time they reach their mid-40s.

FA is caused by a severe deficiency of the frataxin protein inside the mitochondria, the cell's powerhouse. Without frataxin, the body can't produce adenosine triphosphate (ATP), which leads to nervous system damage.

More than a decade ago, Dr. Lynch and colleagues at CHOP were investigating the possibility of targeting the NRF2 pathway, which protects the body against oxidants, as a potential FA treatment. Simultaneously, Texas-based Reata Pharmaceuticals Inc. was investigating a drug that would activate NRF2 — as a potential treatment for cancer. Dr. Lynch and colleagues from the Friedreich's Ataxia Research Alliance (FARA) flew to Plano, Texas, for a meeting with the company, suggesting that it would be worthwhile to pursue the same drug in patients with FA.

With access to the largest number of FA patients in the country, CHOP worked with the company to organize the multisite clinical trials to study omaveloxolone and served as a lead clinical trial site. CHOP enrolled 55 patients between the ages of 16 and 44 into two phases of the clinical trial, which tested the drug's safety and efficacy.

> "COLLEGE STUDENTS WHO WERE SO FATIGUED THAT THEY COULDN'T MAKE IT THROUGH TWO CLASSES A DAY — BECAUSE FATIGUE IS A BIG PART OF FA — AFTER NINE MONTHS ON THE TREATMENT, THEY COULD MAKE IT THROUGH MULTIPLE CLASSES PER DAY WHILE WORKING A PART-TIME JOB." **- DAVID LYNCH, MD, PHD**

The drug was shown to be effective at improving symptoms and slowing the progression of the disease, essentially sending patients back in time, on average, by a year or two and keeping them at that disease state for three to four years.

“Patients realized they could do things they couldn’t do a year ago,” Dr. Lynch said. “College students who were so fatigued that they couldn’t make it through two classes a day — because fatigue is a big part of FA — after nine months on the treatment, they could make it through multiple classes per day while working a part-time job.”

Motivated for a Bright Future

Anna has participated in multiple research studies and clinical trials, including Dr. Lynch’s natural history study, which is funded by FARA. Every year, Anna, her three siblings, and their parents travel together to Philadelphia to participate in rideATAXIA, an annual bike ride to raise funds for FARA’s mission to treat and cure FA through research.

For a study focused on the impact of exercise, Anna followed a specific strength training regimen. Participating in that study helped her establish an exercise routine, and showed Anna how maintaining her mobility and stamina could help slow the progression of FA symptoms.

“The experiences that we have been provided through the Center of Excellence have been absolutely amazing,” Kristin said. “There is so much progress being made. We feel so fortunate to be able to participate.”

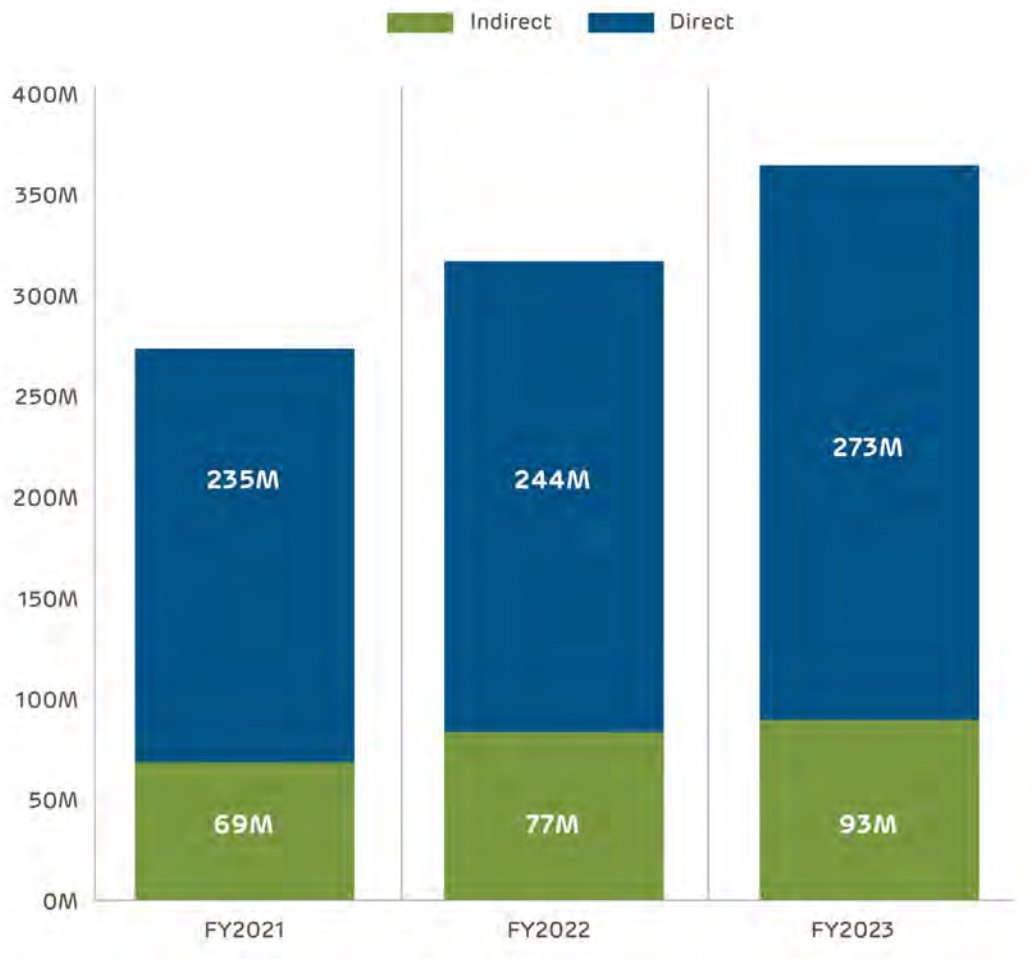
Anna, a junior at an all-girls high school, is passionate about sports and loves to stay busy. After school, she serves as the manager for the lacrosse, basketball, and field hockey teams. She plans to go to college and major in a sports-related field, and she would like to continue participating in FA research and advocacy efforts.

“I think she feels proud to participate in the studies,” Kristin said. “She feels she’s doing her part to further the research.”

2023 RI Annual Report Facts and Figures

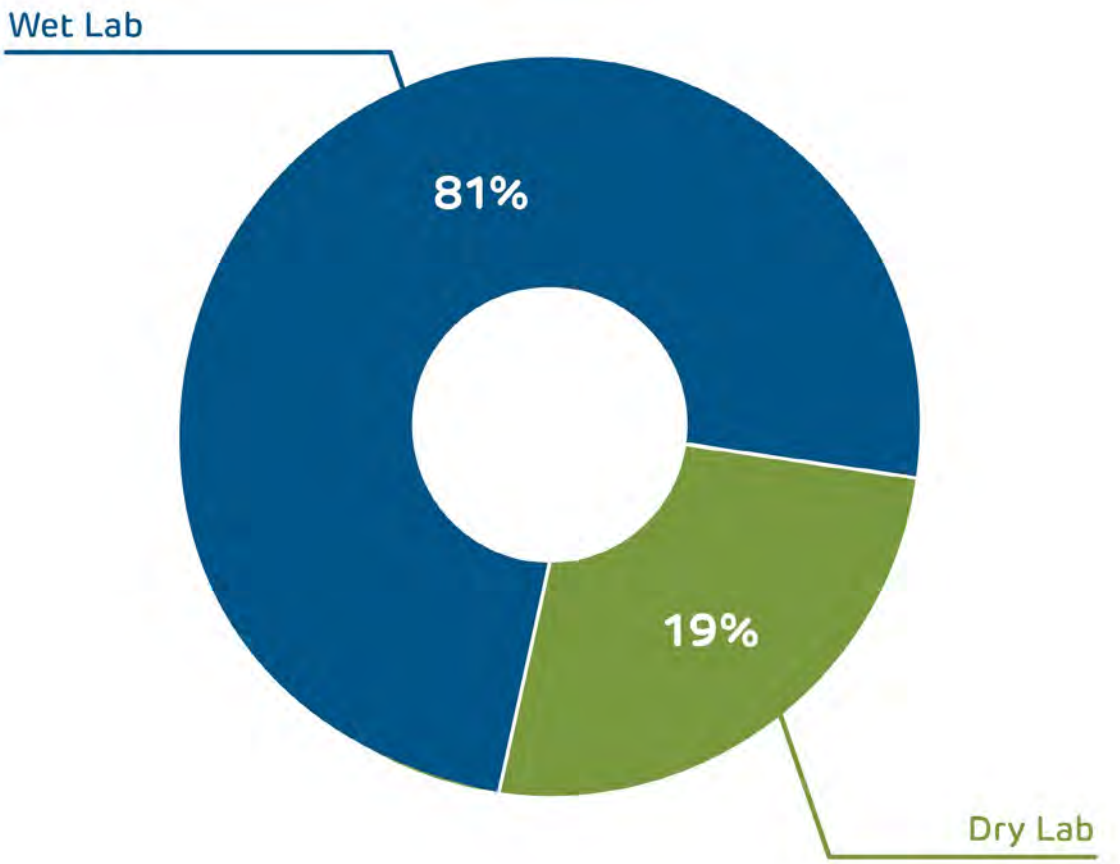
Key Metrics

Total Grant Funding

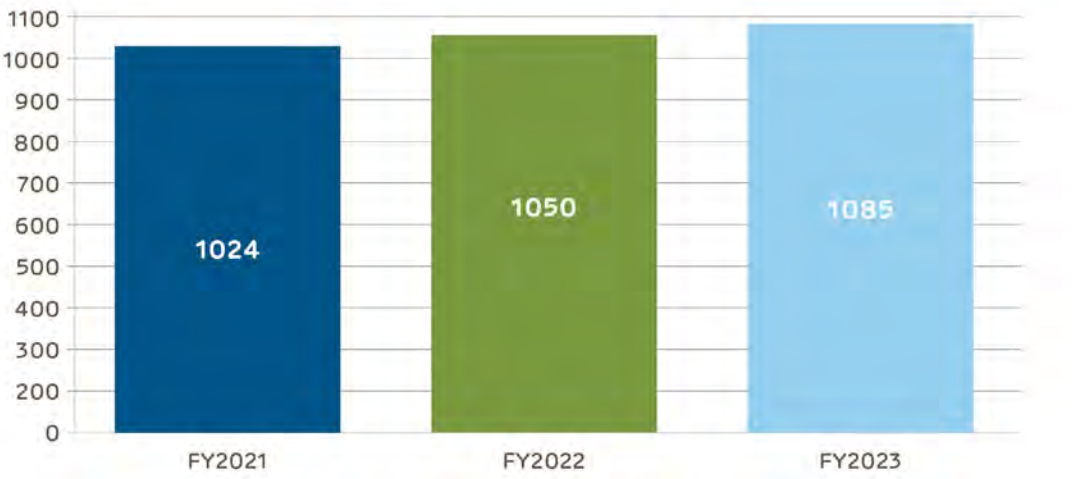


FY2023 Research Space (Sq. Ft.)

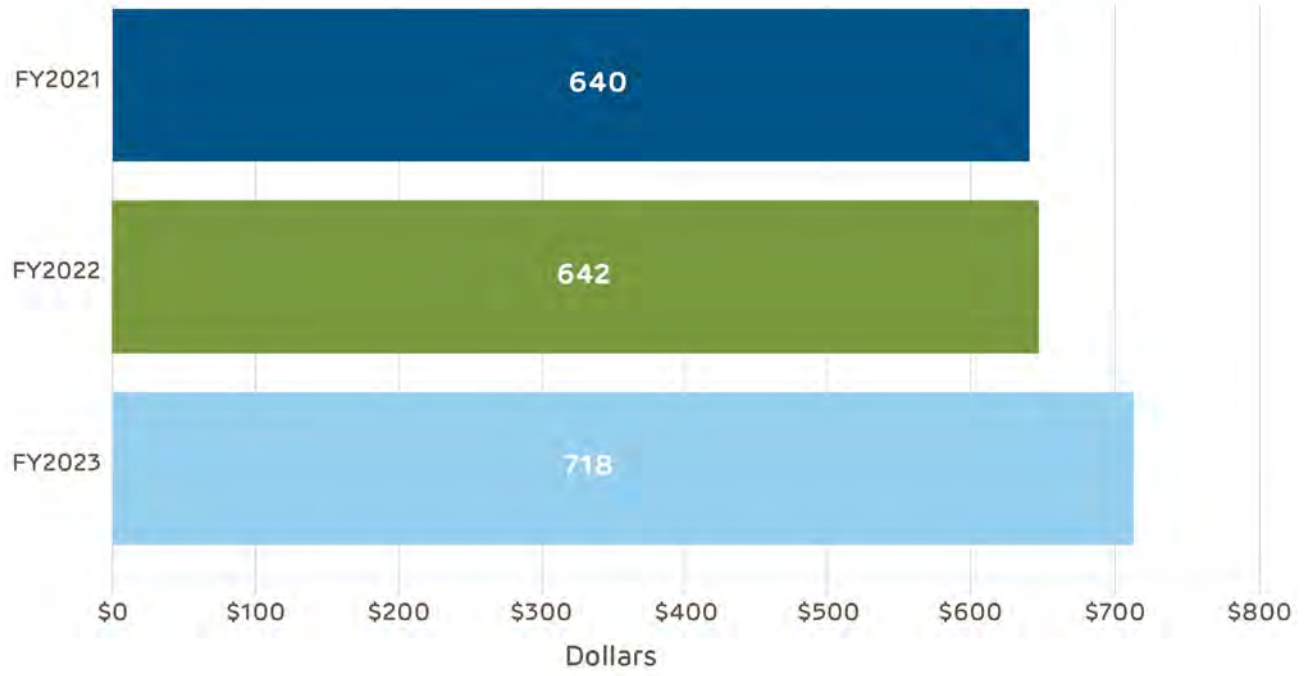
Total: 639K



Number of PI (With Active Grants/Protocols)

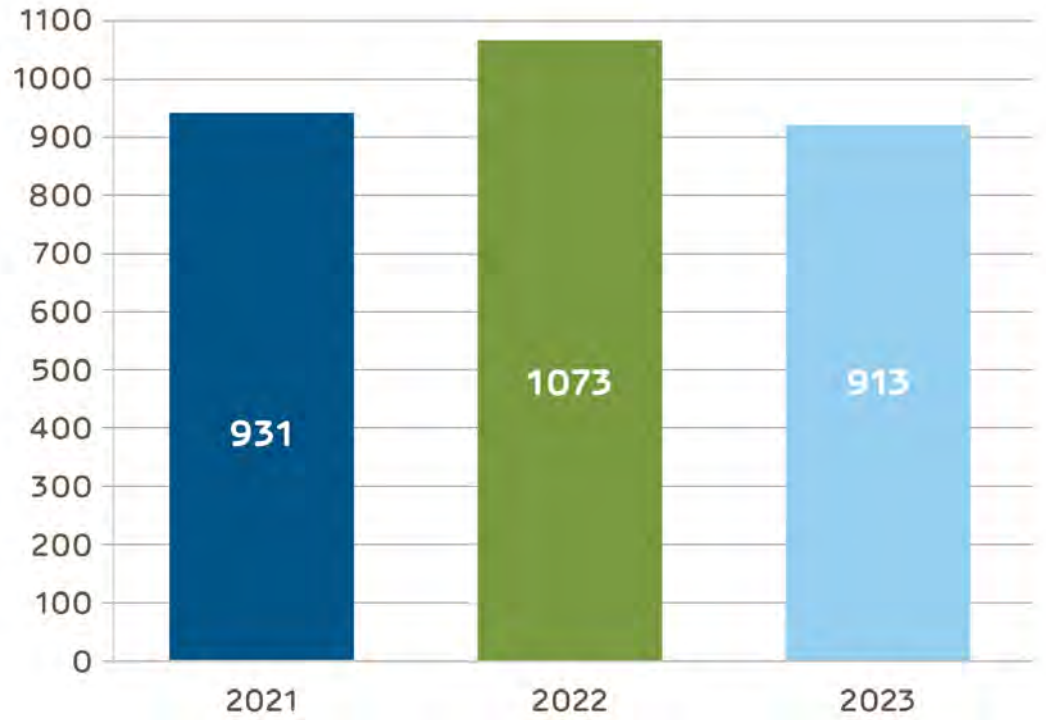


Wet Lab - Average $/Sq. Ft.

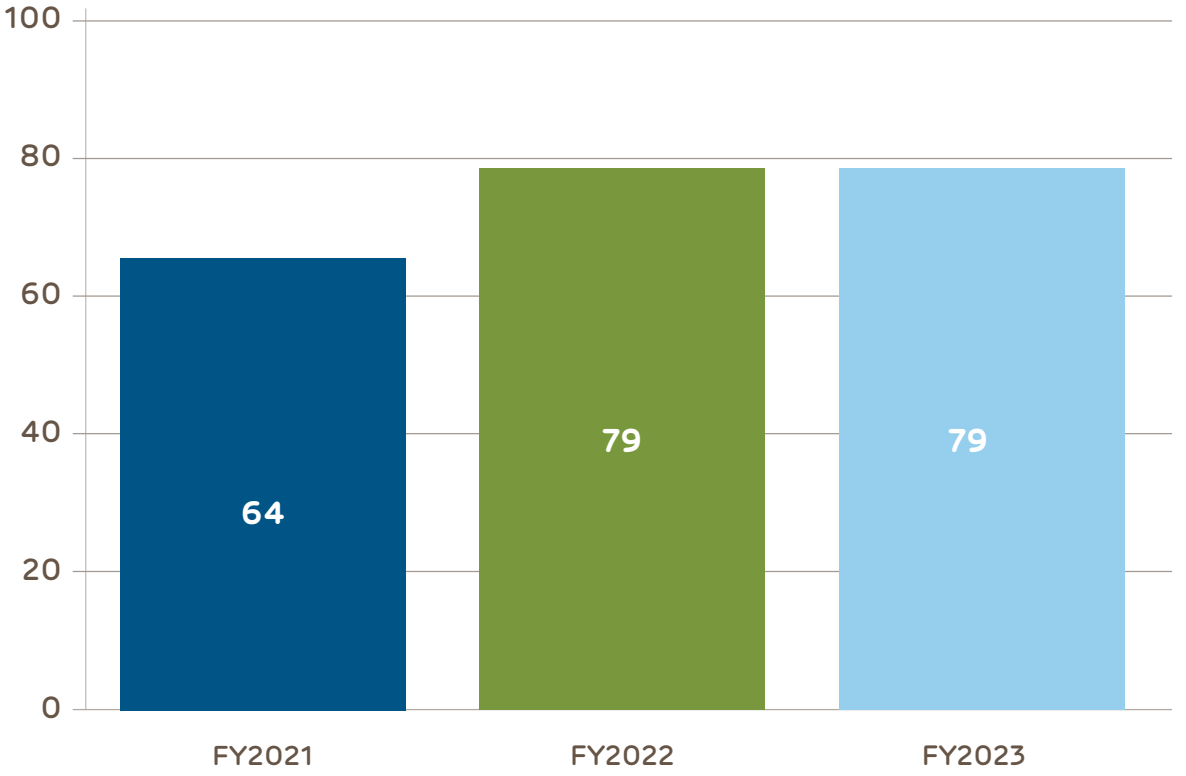


Strategic Impact & Innovation

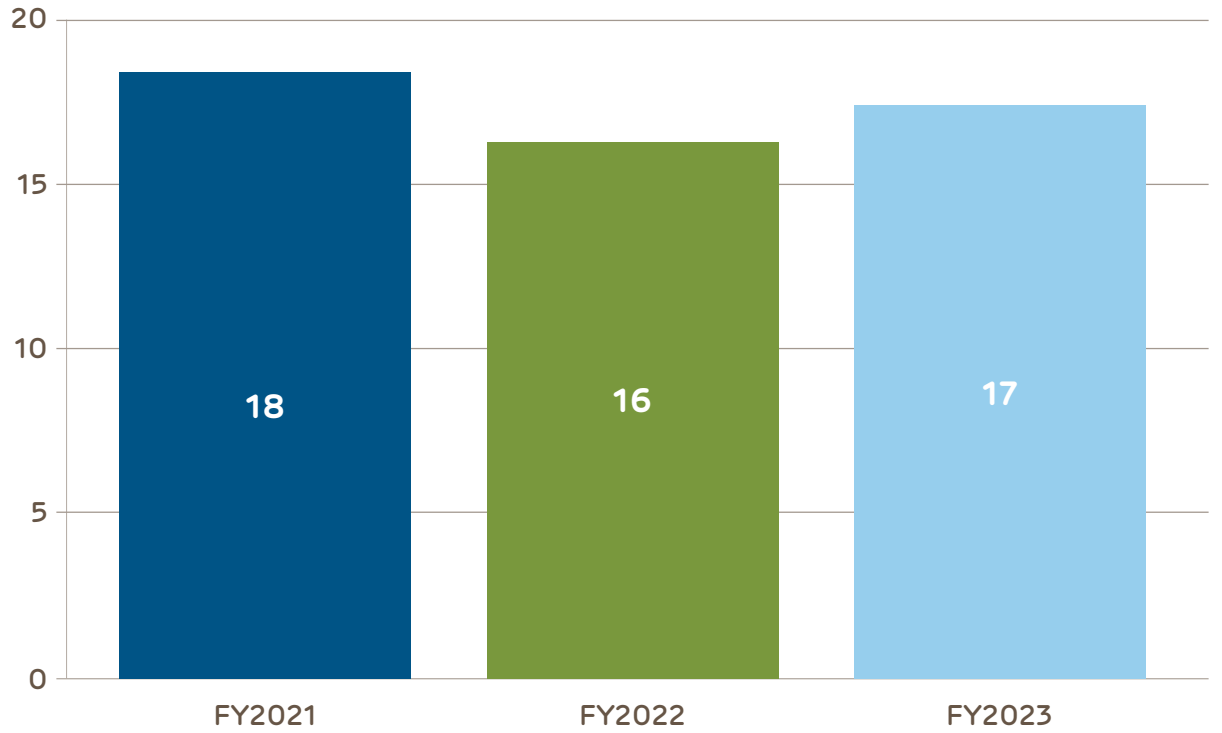
Number of High-Impact Publications
(Calendar Year)



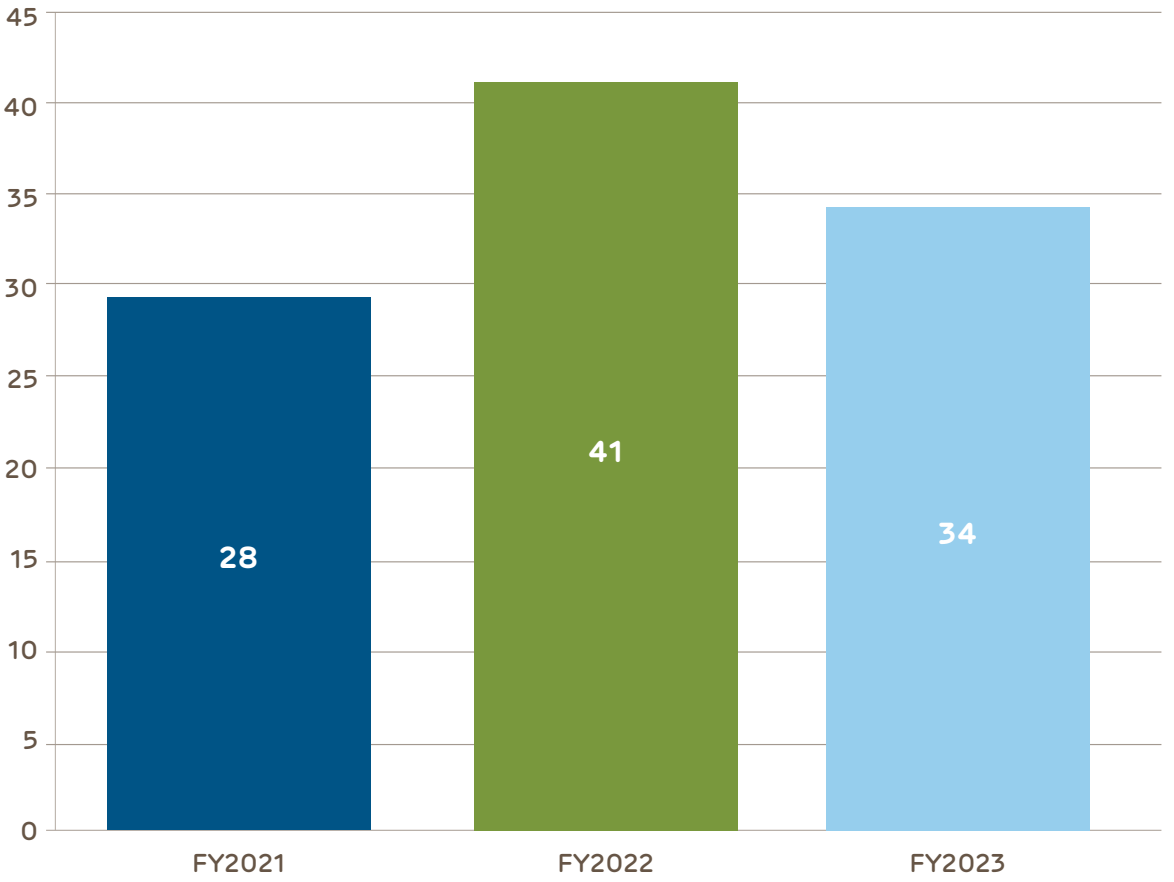
Number of New US Patent Applications



Number of US Patents Issued



Number of US Licenses & Options



Key Strategic Initiatives & Growth

2.43M
OF PATIENTS WITH DATA IN ARCUS

102
OF CAREER DEVELOPMENT AWARDS

23,133
OF PATIENTS WITH GENOMIC DATA IN ARCUS