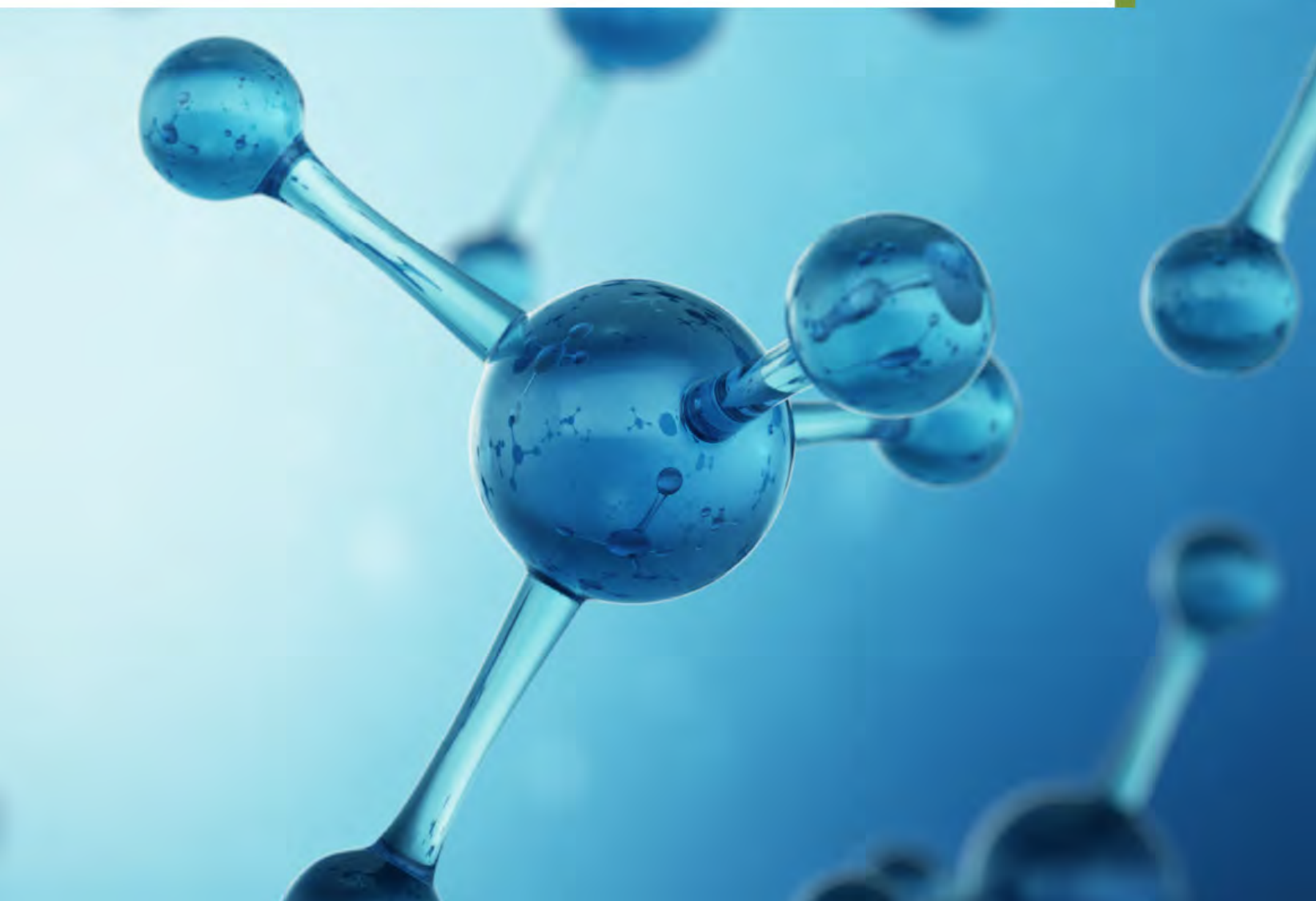


# 2020

## RESEARCH ANNUAL REPORT





## Coming Together to Make a Difference

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The 2020 Research Annual Report highlights remarkable achievements across our scientific pillars: rare and complex diseases, lifespan research, novel therapeutics, precision medicine, and strategy and growth. Don't miss the Inspiration story that celebrates the Research Institute community's resilience, as we safeguarded each other's health during the pandemic and made progress in pediatric science that is changing lives for the better.

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## Researchers Dedicated to Solving Rare and Complex Diseases

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CHOP Research Institute has an unwavering focus on solving the most challenging rare and complex pediatric diseases. In 2020, this led to novel insights and initiatives. Single ventricle heart defects research expanded, thanks to a joint initiative. New grants supported establishment of a Center for Machine Learning in Urology. A Very Rare Malignant Tumors Program launched, and more.

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## ENGIN Links Genetic and Phenotypic Traits in Pediatric Epilepsy




### PRECISION PATH

"Our mantra at ENGIN is that every child with epilepsy should have genetic testing."

of DEE, painting a picture that elucidates the cause of these hard-to-treat brain disorders. In the study that appeared in the [\*American Journal of Human Genetics\*](#), researchers evaluated phenotypic and genetic information collected from several cohorts for more than a decade, and they found 11 genetic causes of specific clinical features.

"What we have done with this study is re-engineered the cognitive process that goes on when clinicians discover a new syndrome," said [Ingo Helbig, MD](#), attending physician at ENGIN, director of the genomic and data science core of ENGIN, and lead investigator of the study. "As the amount of deep phenotypic data available to us increases, we now have the ability to identify novel genetic causes of particularly severe forms of epilepsy that are targets for new treatments."

Soon after its designation as a [CHOP Frontier Program](#) for FY 2020, the [Epilepsy NeuroGenetics Initiative](#) (ENGIN) demonstrated its determination to learn more about developmental and epileptic encephalopathies (DEE). Researchers built upon their previous genomic findings and linked genetic mutations with clinical features



## Researchers Identify Genetic Variation Linked to Inflammatory Bowel Disease

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### PINPOINTING GENETIC MUTATIONS

"Using this method, we believe we have added an important tool to our arsenal of SNP-to-gene assignment methods."

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Researchers in the [Center for Applied Genomics](#) discovered a genetic variation that drives the development of [inflammatory bowel disease](#) (IBD), such as Crohn's disease and ulcerative colitis. Both of these diseases have known genetic components, and more than 240 genetic regions are associated with IBD.

The new findings published in the [Journal of Crohn's and Colitis](#) focus on a single nucleotide polymorphism (SNP) on the *JAK2* gene. The researchers identified two proteins on this SNP that regulate gene expression, and they may serve as a potential therapeutic target for IBD. This genetic pathway is also associated with other immune disorders.

"Using this method, we believe we have added an important tool to our arsenal of SNP-to-gene assignment methods, allowing us to pinpoint disease-driving genetic mutations that have previously been difficult to properly assign risk," said [Hakon Hakonarson, MD, PhD](#), director of the Center for Applied Genomics. "This study in particular also provides evidence that drugs targeting JAK2 may provide some benefit for those patients suffering from IBD who carry mutations that upregulate the JAK2 pathway, though such precision-based approaches would need to be validated in clinical studies."



## Imaging Method Allows 3-D Visualization of Hard-to-View Area of Colon



### NEW INSIGHT INTO CELLS

"We believe our new approach will help us understand bowel diseases in more detail and could lead to new approaches to therapy."

defect that requires surgical repair, and other conditions in which food is unable to move properly through the bowel.

"Having 3-D images of the colon enteric nervous system provides us with new insight into the cells that control bowel function, and may help us better understand disorders of the colon," said [Robert Heuckeroth, MD, PhD](#), a pediatric gastroenterologist in the [Division of Gastroenterology, Hepatology and Nutrition](#) at CHOP, and Research Director and Norman and Irma Braman Endowed Chair of CHOP's [Lustgarten Center for GI Motility](#). "To do this work, we had to invent a new way to make the colon invisible, stain the cells we were interested in seeing, and generate thousands of images."

The findings appeared in [Gastroenterology](#), and the images generated from the study are available on a public database.

A [new imaging method](#) developed by researchers at CHOP helps visualize the enteric nervous system (ENS), a part of the human colon that is typically hard to view. The method combines several techniques and allows the ENS to be viewed in 3-D. The ENS regulates many functions of the bowel, such as the movement of food and nutrients. Defects in the ENS cause Hirschsprung disease, a birth

A person in silhouette, wearing glasses, is looking at a wall of digital data screens. The screens display various charts, graphs, and data visualizations in shades of blue and green. The person's head is in profile, facing right.

## Grants Establish Center for Machine Learning in Urology

A collection of grants are allowing researchers at CHOP to establish a Center for Machine Learning in Urology, with the goal of improving the understanding the pathophysiology, risk stratification, identification of novel therapeutic targets, and prediction of treatment responses of benign urological diseases among children and adults.

[Gregory Tasian, MD, MSc, MSCE](#), attending urologist and associate professor of Surgery and Epidemiology at the Perelman School of Medicine at the University of Pennsylvania, will lead the center, which is a joint venture between CHOP and Penn.

“Over the last five to 10 years, data have become bigger and more complex, and along with that is the challenge of how to efficiently and effectively analyze those data,” Dr. Tasian said. “Machine learning is one of those tools that can handle that complexity. Specifically in urology, there are tremendous knowledge gaps across the lifespan, and many of those knowledge gaps exist because we haven’t had the tools to analyze some of those data.”

In addition to the research goals, Dr. Tasian anticipates the Center will serve as an infrastructure that will allow for the dissemination of the knowledge gained, and it will serve as a forum for mentoring and training at CHOP and other institutions.

## CHOP Launches Very Rare Malignant Tumors Program



### GROUNDBREAKING LEADERSHIP

"With the launch of our Very Rare Malignant Tumors Program, Dr. Laetsch will lead an innovative new program that will develop breakthrough treatments for our patients."

Pediatric hematologist-oncologist [Theodore Laetsch, MD](#), joined CHOP this year, where he will launch the [Very Rare Malignant Tumors Program](#). The purpose of the program is to develop new treatments for children with rare and complex tumors. In pediatrics, rare tumors are generally those that affect fewer than 100 children per year, according to Dr. Laetsch.

"CHOP is a great place for this program because rare tumors span many groups and departments, and the collaboration between the faculty and staff of these programs is what makes it work," Dr. Laetsch said. "We also have a valuable alignment with Penn. Some rare tumors in children, such as colon cancer and ovarian cancer, are more common in adults. We approach treatment of these by working collaboratively with medical oncologists at Penn who are experts in these diseases. It's this overall environment that makes CHOP ideal."

Some of the specific research areas Dr. Laetsch anticipates focusing on are molecular targeted therapies, research into new treatments for thyroid cancer, and translational research in rare subtypes of sarcoma including TRK fusion cancers.

"We want to learn the most we can from our patients and apply that knowledge to future patients," Dr. Laetsch said. "Given the very small number of patients with some of these cancers, it hasn't been possible to define standard treatments. By studying the genetic factors that drive these rare cancers, we are working to identify new treatments to try based on the specific genetic changes in the cancer, regardless of where the tumor arose."





## CHOP Joins Research Collaboration for Single Ventricle Heart Defects

CHOP joined four other research institutions in a large-scale, coordinated research effort to develop new treatments for patients with [single ventricle heart defects](#) (SVDs), thanks to receipt of a [\\$1 million Innovation Fund](#) endowed by Additional Ventures, a nonprofit dedicated to helping children with congenital heart defects. SVDs are rare, affecting about five in 100,000 newborns each year, and they require multiple open-heart surgeries.

CHOP pioneered a surgical technique that is used worldwide for SVDs, and researchers continue to search for ways to improve outcomes in these patients by gaining more understanding of the condition's causes and developing functional cures.

“This joint initiative will fuel breakthrough research that will meaningfully improve the lives of children born with single ventricle defects,” said [Bryan Wolf, MD, PhD](#), Chief Scientific Officer at CHOP. “We look forward to collaborating with these other institutions and continuing the cutting-edge research that has put our Cardiac Center at the forefront of pediatric care.”



## Lifespan Research Aims to Improve Health From Gestation to Adulthood

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Our lifespan research approach focuses on disorders directly affecting the fetus, but also on disorders that first manifest in the child or adult. Highlights from 2020 include progress on identifying genetic determinants for diabetes types, an award to build an evidence-base for prenatal gene editing, and a 10-year study that showed enduring benefits of prenatal surgery for spina bifida.

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## New Innovator Award Advances Research in Prenatal Gene Editing to Treat Congenital Disorders



### POWERFUL GENE-EDITING TOOL

"The ability to cure or mitigate a disease via gene editing in mid-to-late gestation before birth and the onset of irreversible pathology is very exciting."

[William Peranteau, MD](#), an investigator in the [Center for Fetal Research](#), and a pediatric and fetal surgeon in the [Center for Fetal Diagnosis and Treatment](#), received a [highly competitive grant award](#) that will allow his team to [explore the use of prenatal CRISPR-mediated gene therapy in congenital disorders](#). He received \$1.5 million over a five-year period through the NIH Director's New Innovator Award.

Dr. Peranteau's research focuses on using CRISPR — a powerful gene-editing tool that harnesses an enzyme to cut and paste genetic instructions at a precise location in a DNA sequence — to cure or reduce the severity of genetic disorders before birth. He emphasized that much more work needs to be done prior to considering clinical application.

In [related research](#), Dr. Peranteau, also an assistant professor of surgery in the Perelman School of Medicine at the University of Pennsylvania, and collaborators at Penn were successful working with mouse models to correct a harmful mutation before birth by using CRISPR-mediated gene editing. They thwarted a lethal lung disease, surfactant protein deficiency, in which death occurs within hours after birth. This [proof-of-concept study](#) appeared in *Science Translational Medicine*.

"The ability to cure or mitigate a disease via gene editing in mid-to-late gestation before birth and the onset of irreversible pathology is very exciting," Dr. Peranteau said in a press release at the time of publication. "This is particularly true for diseases that affect the lungs, whose function becomes dramatically more important at the time of birth."

The New Innovator Award will allow his team to explore prenatal CRISPR gene editing in other congenital disorders.

## Genetic Differences Help Distinguish an Adult-onset Form of Diabetes and Type 1 Diabetes in Children



### NEW GENETIC SIGNATURE

"This is our first insight into genetic differences between latent autoimmune diabetes in adults and T1D in children that may be diagnostically useful."

may allow clinicians to diagnose LADA using a genotype array instead of a complex and expensive autoantibody screening.

LADA, also referred to as type 1.5 diabetes, shares characteristics with both T1D and type 2 diabetes (T2D); however, from a genetic perspective, CHOP researchers previously found LADA has more in common with T1D than with T2D. The new findings, published in the journal [Diabetes Care](#), took a deeper dive into LADA's distinguishing differences, opening the door to more straightforward diagnostic tests and improved responses to appropriate treatments.

One of those differences identified by the research team is that they did not observe genetic associations with the major histocompatibility complex (MHC) in patients with LADA. MHC is a highly variable region of the genome that helps drive the immune system and is implicated in T1D.

"This suggests that these MHC class associations may be a genetic discriminator between LADA and childhood-onset T1D," said Diana Cousminer, PhD, a geneticist at CHOP and a joint-first author of the study. "The next step is to look at this association in different ethnicities, particularly African ancestry, where the prevalence of adult-onset diabetes can be significantly higher in certain parts of the world."

CHOP researchers gained insights into genetic differences between latent autoimmune diabetes (LADA) in adults and type 1 diabetes (T1D) in children that may be diagnostically useful, according to study leader [Struan Grant, PhD](#), co-director of the [Center for Spatial and Functional Genomics](#) at CHOP and the Daniel B. Burke Endowed Chair for Diabetes Research. The new genetic signature

## Follow-up Research to Landmark MOMS Study Shows Ongoing Benefits of Prenatal Surgery for Spina Bifida

### LONG-TERM GAINS

"It is extremely gratifying to see that the positive results from the initial MOMS trial endure into childhood."

Results from the "MOMS2: Follow-up of the Management of Myelomeningocele Study," published in [\*Pediatrics\*](#), [showed significant physical and emotional benefits in school-age children](#) who received corrective surgery in the womb for MMC, the most severe form of spina bifida.

"It is extremely gratifying to see that the positive results from the initial MOMS trial endure into childhood," said [N. Scott Adzick, MD, MMM](#), CHOP's Surgeon-in-Chief, who first performed fetal surgery to repair spina bifida in 1998 at CHOP's [Center for Fetal Diagnosis and Treatment](#). "Fetal surgery is a complex and serious procedure and should only be done by experienced teams. Research needs to continue to refine the technique in a way that will improve outcomes even further."

Although there was no significant difference in overall adaptive behavior or cognitive benefits between children who had prenatal surgery for spina bifida compared to children who had surgery after birth, motor function and quality of life were better among children in the prenatal surgery group. Long-term gains included improved mobility and independent functioning in school age children. Walking unassisted, better gross and fine motor skills, improved bladder and bowel control, and fewer surgeries for shunt placement and revision were among the benefits. In addition, the children and families in the prenatal group reported less stress on the family overall.

In 2011, [results of the original landmark study](#) "MOMS: Management of Myelomeningocele Study" also led by Dr. Adzick, appeared in the *New England Journal of Medicine*.





## CHOP Joins Genome to Mental Health Consortium

### FILLING A KNOWLEDGE GAP

"We are pooling our resources and working as a network to speed things along, in the hope that the greater number of participants the better insight we'll have..."

The [Genome to Mental Health consortium](#) is a new collaboration between researchers at CHOP and 13 institutions worldwide to study the link between rare genomic disorders and psychiatric and developmental conditions. [Donna McDonald-McGinn, MS, LCGC](#), director of the [22q and You Center](#) at CHOP, is leading the initiative at CHOP.

"This project is funded to not only examine the chromosome 22q11.2 deletion, but also 22q11.2 duplication, which is highly associated with autism, and other copy number variants, such as 16p11.2 deletion and duplication," said McDonald-McGinn, who is also a clinical professor of Pediatrics at the Perelman School of Medicine of the University of Pennsylvania. "These conditions are the result of extra or missing pieces of chromosomes, leading to extra or missing copies of genes and resulting in behavioral differences."

The [Genome to Mental Health](#) researchers will be examining multiple phenotypes, including psychosis, anxiety, ADHD, depression, and autism, to determine their prevalence and to identify specific genes within the copy number variants that may contribute to how patients present and how the longitudinal disease course will progress. Ultimately, their aim is to inform early detection of these conditions and their associated features, as well as to identify biologic targets that could be used to develop novel therapeutics for these patients.

## Study Team Develops Autism-specific Lifespan Quality of Life Measurement Tool



### IMPORTANT FOUNDATION

"This study demonstrated that assessing quality of life among patients of different ages and genders is possible, and that it's meaningful."

A set of simple questionnaires can help clinicians and families [evaluate better the quality of life of people diagnosed with autism spectrum disorder](#) (ASD), according to a study led by CHOP researchers. The newly developed tool, [PROMIS Autism Battery – Lifespan \(PAB-L\)](#), is designed for children, adolescents, and adults on the autism spectrum. It focuses on five domains: subjective well-being, relationships, emotional distress, health, and adulthood.

A total of 912 participants completed the tool's surveys online. The study measured feasibility, and participants reported that the survey was easy to understand, covered important topics, and may even change the way an individual or parent manages their autism support programs or clinical care based on the results.

"This study demonstrated that assessing quality of life among patients of different ages and genders is possible, and that it's meaningful," said [Judith S. Miller, PhD](#), a psychologist in the Department of [Child and Adolescent Psychiatry and Behavioral Sciences](#), a senior scientist and training director in the [Center for Autism Research at CHOP](#), and senior author of the study. "We believe that these findings provide an important foundation to answer some very important questions about how to support the quality of life for people with autism, including those who have been historically underrepresented in clinical research."

The study appeared in [Autism Research](#).



## Life-changing and Practice-changing Novel Therapeutics Advance

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Don't miss the many novel therapeutics under development that Research Institute scientists reported on their success and advancements in 2020, including the first-ever treatment for peanut allergies. Learn about practice-changing findings for pediatric acute myeloid leukemia therapy. Find out why an intriguing idea to transform sepsis treatment grabbed the NIH director's attention.

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## U.S. Food and Drug Administration Approved First-ever Oral Immunotherapy to Treat Peanut Allergies



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### FIRST OF ITS KIND

"For many patients, [this medication] opens up their lives tremendously."

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to accidental exposure for many children managing peanut allergies — of which there are 1.2 million children in the United States.

The U.S. Food and Drug Administration approved the [first-ever treatment for peanut allergies](#), an oral immunotherapy that researchers in our [Allergy Section](#) have worked over a decade to help develop. While the medication is not a cure-all, [Jonathan Spergel, MD, PhD](#), section chief of [CHOP's Food Allergy Center](#), said it may minimize severe reactions

"For many patients, [this medication] opens up their lives tremendously," Dr. Spergel said. "They're able to go out to dinner, or go out to a ballgame, or travel with a lot less anxiety. It gives them some level of confidence, and for many patients, it's really opened up the door to do many things restricted to them in the past. For patients who have done well, it's been truly life changing."

Children and young adults ages 4 to 17 are eligible for the drug, which pharmaceutical company Aimmune Therapeutics manufactures. Previously, no treatments for peanut allergies existed, save for avoiding peanuts altogether. And despite a parent or caregiver's best attempts to monitor what their child consumes, reactions to peanut allergies still send one in four children to the emergency room every year.

## Dexrazoxane Lowers Risk for Cardiotoxicity Associated With Chemotherapy in Pediatric Acute Myeloid Leukemia

### SHIFTING STANDARD OF CARE

"These findings are practice-changing..."

AML, researchers found that pre-treatment with dexrazoxane before each round of anthracycline chemotherapy [helped mitigate cardiotoxicity often associated with the treatment](#).


Dexrazoxane also was linked to lower treatment-related mortality, and it did not increase other non-cardiac toxicities. The study appeared in the [Journal of Clinical Oncology](#).

[Richard Aplenc, MD, PhD, MSCE](#), led the Children's Oncology Group (COG) study. Dr. Aplenc is assistant vice president and chief clinical research officer at CHOP, professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania, and core faculty member of the [Center for Pediatric Clinical Effectiveness](#) (CPCE) at CHOP. First author [Kelly D. Getz, PhD, MPH](#) is also a core faculty member of the CPCE at CHOP, and assistant professor of Epidemiology at Penn.

"We demonstrated the benefit of dexrazoxane with respect to the cardioprotection and secondarily, the suggestion of a lower treatment-related mortality," Dr. Getz said. "These findings are practice-changing: The upcoming COG Phase III clinical trial for AML will include a requirement to administer dexrazoxane for cardioprotection to patients receiving standard anthracycline chemotherapy."

Curative therapy for pediatric acute myeloid leukemia (AML) involves high doses of anthracycline chemotherapy. Although this treatment is highly effective at killing cancer cells, it is also highly cardiotoxic. In a study of more than 1,000 pediatric patients with





## Researchers Create Stickier Neutrophil Extracellular Traps to Improve Sepsis Treatment

### NOVEL APPROACH

"Given that the treatment was most effective when combined with antibiotics, it's possible that these two treatments may act synergistically to lead to better outcomes."

infection and a leading cause for hospital death.

A team of researchers [enhanced the body's bacteria-capturing neutrophil extracellular traps \(NETs\)](#) by adding a protein called platelet factor 4 that binds to the NETs and makes them better at catching and holding onto bacteria. This approach could transform the way clinicians treat sepsis in the future and could have implications for the treatment of other immune conditions in which NETs are involved. [Sepsis](#) is a deadly complication of

"These results indicate that our NET-stabilizing interventions enhance that ability of NETs to capture bacteria while preventing them from releasing antibacterial compounds that can cause organ damage, dramatically improving bacterial clearance as well as survival in a mouse model of sepsis," said [Kandace Gollomp, MD](#), physician researcher in the Division of Hematology and first author of the paper. "Given that the treatment was most effective when combined with antibiotics, it's possible that these two treatments may act synergistically to lead to better outcomes."

The findings appeared in the journal [Blood](#), and the study team presented them as an abstract at the [61st American Society of Hematology annual meeting](#), where the work was one of the highest scoring abstracts among a group of more than 4,500 submissions. The researchers' idea to make NETs even stickier to catch more bacteria also caught the attention of the National Institutes of Health Director Francis Collins, MD, PhD, who covered the study in his blog post "[Building a Better Bacterial Trap for Sepsis](#)."

## Novel Prodrug-based Delivery Strategies Aim to Overcome Drug Elimination and Resistance in Cancer Therapy



Investigator [Michael Chorny, PhD](#), received support from the National Cancer Institute for a [collaborative effort](#) with [Garrett Brodeur, MD](#), director of the [Cancer Predisposition Program](#), and [Ivan Alferiev, PhD](#), research associate professor of Pediatrics, to evaluate and optimize a novel prodrug-based delivery strategy for tumor-specific pharmacotherapy of neuroendocrine cancers.

A prodrug is a medication that is inert until it is converted by the body into a pharmacologically active drug. The prodrug design will be a tool for achieving high selectivity and potency of a chemotherapeutic, while protecting normal tissues from toxic drug exposure.

“The drug itself is chemically optimized to overcome drug elimination and drug resistance,” Dr. Chorny explained. “The end result is more drug to the tumor, and less to the patient.”

The researchers hope this project will facilitate the development, translation, and clinical implementation of targeted prodrugs for treating high-risk neuroblastoma and other aggressive solid tumors that currently lack effective treatment options.

In a related [breakthrough study](#), the research team engineered a prodrug in their lab that led to long-term remissions in 80 percent to 100 percent of mice with drug-resistant or high-risk solid tumors. The findings, which could soon lead to clinical trials, appeared in [Cancer Research](#), a journal of the American Association for Cancer Research.



## Investigators Successfully Apply a Gene Therapy to Correct Defective Genes Throughout the Brain

### REFINING GENE-DELIVERY

"It's a big advance."

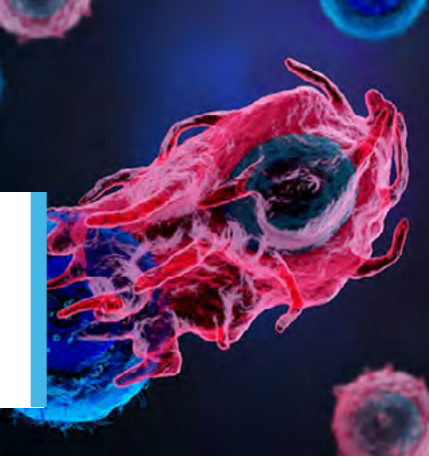
A team of CHOP-Penn investigators successfully delivered [a gene therapy using a viral vector capable of crossing the blood-brain barrier](#) and found evidence that the corrected gene had distributed to various parts of the brain, including the cerebral cortex, hippocampus, and mid-brain.

[John Wolfe, VMD, PhD](#), a researcher at CHOP and the University of Pennsylvania's School of Veterinary Medicine and the Perelman School of Medicine, worked with a large animal model of a type of lysosomal storage disease, alpha-mannosidosis. This inherited condition causes severe disease of the brain, naturally occurs in this animal model, and results from a mutated copy of the alpha-mannosidase gene.

"This is the first example of a large-brain mammal with a *bona fide* human genetic disease that has intellectual disability as part of the human syndrome where we've been able to correct the biochemistry and pathologic lesions in the whole brain," said Dr. Wolfe in a *Penn Today* article. "It's a big advance. Nobody has been able to treat the whole brain of a large-brained animal before. We're hopeful that this will translate into clinical use in humans."

The [study findings](#) appeared in *Brain*, a journal of neurology.

## Proposed First-in-Class Therapy Holds Potential to Have Broad Effect on Treatment of a Variety of Cancers



### ON A FAST TRACK

"What makes our proposed therapy unique is that it simultaneously targets multiple pathways, attacking cancer cells from various immunostimulatory angles..."

Ian Henrich, PhD, a postdoc researcher in the Department of Pathology and Laboratory Medicine at CHOP, is one of three recipients of the University Science Center's [QED Proof-of-Concept Program](#) award. Dr. Henrich is collaborating with [Margaret Chou, PhD](#), a cancer researcher, [to investigate the effects of USP6](#), a protein that optimizes a patient's immune response, on acute myeloid leukemia (AML), the second most common blood cancer.

At the end of the one-year QED period, Drs. Chou and Henrich aim to have a final phase product — a nanoparticle delivering USP6 that can be targeted to the AML cancer cell with verified activity in animal models that will lead to future clinical trials. The researchers are confident USP6-related therapy will have implications beyond AML. USP6 simultaneously targets multiple pathways, attacking cancer cells from various immunostimulatory angles, which helps prevent them from building resistance.

"Not only do we envision that the USP6 nanoparticle therapy could act as the standalone agent in combating cancer, we think it can greatly increase the number of patients who can respond to existing immunotherapies," Dr. Chou said.



## Precision Medicine Shaping Next Generation of Breakthroughs

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Our investigators incorporate cutting-edge approaches in gene therapy, genomics, diagnostic imaging, and data analysis to dive deeper than ever before into individualized medicine. In 2020, we took this commitment to the next level by creating the Cell and Gene Therapy Collaborative to promote collaboration across the Research Institute and shape the next generation of breakthroughs.

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## Cell and Gene Therapy Collaborative Driving Research Forward

Children's Hospital of Philadelphia aspires to be the global leader in pediatric and cell gene therapy discovery and treatment while continuing to shape the next generation of breakthroughs.

The Cell and Gene Therapy Collaborative (CGTC) was established in 2020 to cultivate support for more CHOP-led research and to accelerate the pace of clinical development, in order to provide new therapies to children. The Collaborative will advance CHOP preclinical and clinical infrastructure in support of its vision.

Importantly, the CGTC will promote and foster continued collaboration and partnership across many areas of the Research Institute including the [Raymond G. Perelman Center for Cellular and Molecular Therapeutics](#), the [Cellular Therapy and Transplant Section in the Division of Oncology](#), the [Department of Pathology and Laboratory Medicine](#), the [Division of Human Genetics](#), the [Center for Applied Genomics](#), the [Center for Fetal Research](#), and faculty members from research and clinical programs across the institution who contribute to this work.

Additionally, two CGTC grant programs support the development of promising cell and gene therapy programs from concept to clinical trial. [Seed Grants](#) promote early stage development of new ideas with the ultimate goal of preclinical proof of concept. [Acceleration Grants](#) support later-stage programs as they advance toward first-in-human testing.



## Roberts Individualized Medical Genetics Center Provides a Model to Emulate

### CENTRALIZED MODEL

"The RIMGC is the first-of-its-type built in a focused way in the country in a pediatric setting."

The [Roberts Individualized Medical Genetics Center \(RIMGC\)](#) is a first-of-its-kind system to help families navigate the complex process of genetic and genomic testing and standardize how genetic testing is performed across different clinical disciplines. In a special report published in [Pediatrics](#), RIMGC researchers, physicians, and [counselors](#) [described the success of the model](#), their plans for the future, and important lessons learned. The team also provided a framework for making such a center work, as other hospital systems seek to replicate the model established at CHOP.

"We are deeply thankful to the Roberts family, whose generous support has pioneered the cutting-edge work we are doing in the RIMGC," said [Ian Krantz, MD](#), director of the RIMGC.

The report included five complex case studies of patients with medical conditions that were properly diagnosed thanks to the resources provided by RIMGC. One of them is the journey of [Athan Fullam](#), who spent his first three months in the NICU receiving multiple, daily blood platelet transfusions, while his parents endured the uncertainty of tests that yielded no answers.

His diagnostic break came after Athan underwent whole exome sequencing and was found to have NLRC4-MAS, a novel, primary autoinflammatory syndrome caused by mutations in the NLRC4 gene. He is only the 21st patient to be identified with this rare, life-threatening condition. Athan began a clinical trial medication the next day, and his overall health took a positive turn.



## Image-based Precision Medicine Leverages Virtual Reality Capabilities

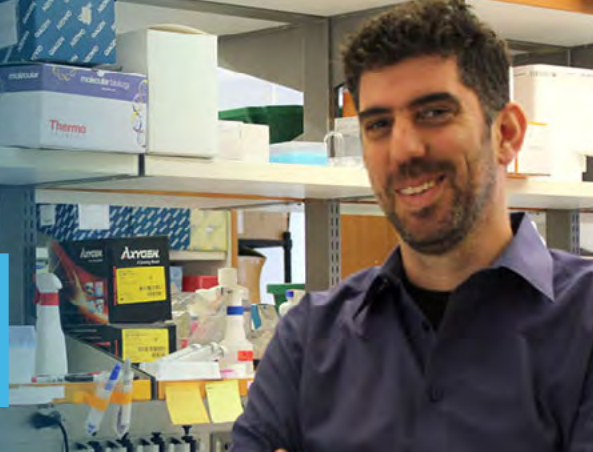
The [Cardiac Center](#) is exploring the potential of virtual reality (VR) from the lab to the bedside. An innovative collaboration with diagnostic imaging experts enables cardiac clinicians to review echocardiograms, CTs, and MRIs in the 3D Imaging Review Suite using SlicerVR software. The results are 3D models that clinicians can resize, interact with, “hold” in their hand, and even step into. Surgeons can view heart anatomy from multiple angles and perspectives prior to surgery, preventing additional, unexpected procedures.

Clinician-researchers like [Matthew Jolley, MD](#), cardiac anesthesiologist and SlicerVR developer, are leveraging VR capabilities to develop novel interventions and deliver individualized, precision care. Dr. Jolley [received a grant to create tricuspid valve computer modeling methods](#) and apply them to a large cohort of patients with hypoplastic left heart syndrome (HLHS). Characterized by incomplete development of the left heart, HLHS affects more than 1,000 live-born infants in the United States annually. This study will delineate the relationship between 3D tricuspid valve structure and valve dysfunction in HLHS, as well as design of patient-specific repairs informed by 3D structural analysis.

“Every kid is unique,” Dr. Jolley said. “Their images are unique. If you distill what we’re doing here, it’s image-based precision medicine.”

VR also enables more thorough medical education through a digitized registry that can be shared across institutions for the benefit of pediatric heart patients all over the world. Researchers in the [Pediatric Heart Valve Center](#) also hope to leverage VR in the development of a curated database that may one day inform valve repairs in patients with rare heart defects.

## Investigating Applications for Precise Gene Tagging



### HIGH RISK AND HIGH REWARD


"The advantage of this novel screening method is that proteins are targeted in a very rapid manner."

function, and a high-resolution study of protein unfolding that is associated with many human diseases. He was one of the pioneers in using the CRISPR system to develop genome-wide loss-of-function screens in mammalian cells.

The new approach will address some of the limitations of existing approaches used by scientists to identify and investigate candidate genes.

"This [research] is 'high risk and high reward' because it requires a significant amount of technological advances that currently do not exist — we need to develop a whole new set of tools," said Dr. Shalem of his project, Direct and Rapid Control of Proteins at Scale. "Once everything is assembled together and successful, this novel screening method can be applied to a very, very wide range of possible questions."

[Ophir Shalem, PhD](#), of the [Raymond G. Perelman Center for Cellular and Molecular Therapeutics](#), received a [high-risk, high-reward grant to develop new functional genomics tools](#) that use precise gene tagging to enable parallel measurements of gene expression dynamics for thousands of proteins, direct and rapid control of protein



## New Computational Tool Helps Researchers Understand Noncoding Mutations

### TARGETS FOR FUTURE RESEARCH

**"If we can understand noncoding mutations better, we can stratify patient subgroups and identify new subgroups."**

Noncoding regions that comprise the majority of the human genome involve structural variants that are large, complex genomic alterations that act as on/off gene-control switches. In cancer, which involves uncontrolled growth and division of cancer cells, noncoding mutations can play important roles as enhancers/promoters to oncogenes or tumor suppressor genes.

A CHOP-Penn study team developed a new computational algorithm called [PANGEA \(predictive analysis of noncoding genomic enhancer/promoter alterations\)](#) that helps scientists characterize a full spectrum of recurrent noncoding mutations. Researchers used the approach to identify and systematically prioritize 1,137 structural variants that may be causal noncoding mutations influencing the expression of more than 2,000 genes across five major types of pediatric cancers. Their analysis also revealed that coding and noncoding mutations affect distinct sets of genes and pathways, with little overlap.

"Because 95 percent of the genome is noncoding, presumably there will be a lot of driver noncoding mutations," said [Kai Tan, PhD](#), professor of Pediatrics, investigator with the Department of Biomedical and Health Informatics, and senior author of the study. "If we can understand noncoding mutations better, we can stratify patient subgroups and identify new subgroups. Even better, if you combine coding mutations and noncoding mutations, maybe we can find good targets for future research and therapy to move into clinical practice."

[PANGEA](#) enables researchers to expand the types of pediatric cancer they can study, identify more noncoding mutations associated with these cancer types, and facilitate future experimental work to characterize and validate predictions about their oncogenic roles.





## Collaboration Key to Empowering Growth and Innovation

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The Research Institute continues to fuel growth and innovation with newly named Frontier Programs and Centers of Emphasis. CHOP's Center for Health Equity aims to dismantle systemic racism. A Drexel University partnership opens opportunities to spur scientific rigor, while the Innovation Ecosystem bridges silos, and Arcus accelerates pediatric research with responsible use of data science.

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**30** Center for Health Equity Will 'Make the Changes We Need to See'

**31** New Frontier Programs Pioneering Advances in Children's Health

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## Center for Health Equity Will 'Make the Changes We Need to See'



The Center for Health Equity was created this year as part of an expanded commitment from CHOP to help dismantle systemic racism, to close the gaps in health and well-being that exist among the children of Philadelphia, and to build a diverse and inclusive team who will champion these efforts. A search is underway for a leader of the Center who will focus on developing clinical programs based on research to promote health equity. By working closely with others at CHOP and in the community, the new Center for Health Equity team will aim to improve the conditions for children and families in areas such as housing, employment, education, criminal justice, and environmental and public health.

“We believe that the Center for Health Equity will help us make the changes we need to see in our community — and in our country,” wrote [Angela Ellison, MD, MSc](#), search committee chair, director of Research, Division of Emergency Medicine, and assistant vice president of Medical Staff Diversity and Inclusion; and [Gilbert Davis, MHA](#), vice president and chief diversity officer, in a letter to the CHOP community. “We look forward to working with the Center’s director — and the CHOP community — to create a healthy, just, and equitable society in which all children have the opportunity to reach their full potential.”

## New Frontier Programs Pioneering Advances in Children's Health



Frontier Programs differentiate CHOP because of their unique combination of translational research and exceptional clinical care of children with highly complex conditions. Three new programs received this designation for FY 2021: the Minds Matter Concussion Program, the Center for Pediatric Heart Valve Disorders, and the Thyroid Center.

The [Minds Matter Concussion Program](#), located within the [Center for Injury Research and Prevention](#), developed a comprehensive clinical assessment of concussions, while introducing aerobic treatment therapies and vestibular and visual rehabilitation. Led by [Christina Master, MD](#); and [Kristy Arbogast, PhD](#), the research team will build on their progress to date by introducing preinjury testing to assess concussion susceptibility and implement clinical diagnostic tools to objectively phenotype concussions, in order to prescribe personalized novel treatments.

Globally, congenital heart defects are the most common birth defect. However, there is no therapy to mitigate valve regurgitation in newborns and infants, nor a valve replacement option that would eliminate the need for redundant surgery as the patient ages. The [Center for Pediatric Heart Valve Disorders Frontier Program](#), led by primary investigators Jonathan Chen, MD; Michael Quartermain, MD; and Matthew Gillespie, MD; aims to answer these unmet needs. The researchers strive to do this by providing coordinated care for pediatric valve patients, delivering novel imaging platforms to refine patient-specific modeling, offering personalized valve therapies to treat the individual patient's needs, and defining therapeutic drug targets to mitigate the progression of the disease.

[The Thyroid Center](#) at CHOP is recognized as the leading center for the treatment of pediatric thyroid disorders in the country, and it is the only center in the United States with a supporting translational research program. Its thyroidectomy surgery outcomes are unparalleled, with astonishingly low complication rates. With [Andy Bauer, MD](#); [Sogol Mostoufi-Moab, MD, MSCE](#); and Aime Franco, PhD; leading this Frontier Program, the Thyroid Center will build on this reputation by defining the molecular landscape of pediatric thyroid cancer, confirming targets of diagnosis, determining markers of invasive behavior, and building a global thyroid community focused on advocacy and education.



## Two New Centers of Emphasis Established: Resuscitation Science Center and Center for Single Cell Biology

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### INDIVIDUALIZED CPR

"The investment in the new Center for Resuscitation Science and the focus on resuscitation and CPR, illustrates how CHOP is pushing the cutting edge every single day."

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anesthesiologist and critical care physician; and [Robert Sutton, MD, MSCE](#), a critical care physician. Dr. Kilbaugh will direct basic science and translational research conducted at the Center, while Dr. Sutton will take the lead for clinical research.

With a syndicate of researchers across the CHOP and University of Pennsylvania campus, coordinated research interests span from therapeutics to mitochondrial genomics, neurodiagnostics, computational biology, and medical countermeasures for chemical and biological threats. Promising findings in the translational space will be put into clinical practice so that all children may benefit. Critical clinical research projects underway include developing and evaluating algorithms using artificial intelligence / machine learning analytics to improve resuscitation monitors and devices, and determining if patient physiology focused resuscitation training can improve pediatric cardiac arrest outcomes.

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### FAST-EVOLVING RESEARCH

"There is a scientific need to develop effective treatments and drug targets based on individual cell types."

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The [Resuscitation Science Center](#) is a multi-faceted collaborative scientific platform dedicated to understanding critical illnesses and accelerating discoveries to improve resuscitation care and outcomes for our sickest children. The new Center will help to position CHOP Research Institute as the world's preeminent clinical and translational critical illness research epicenter. At the helm are CHOP doctors [Todd Kilbaugh, MD](#),

and [Robert Sutton, MD, MSCE](#), a critical care physician. Dr. Kilbaugh will direct basic science and translational research conducted at the Center, while Dr. Sutton will take the lead for clinical research.

The [Center for Single Cell Biology](#) (CSCB) aims to use the precision of single cell technology to take a deep look into the cellular path of multiple diseases such as cancer, lung disease, neurological disease, and metabolic disease to ultimately, improve outcomes for our pediatric patients. Led by [Kai Tan, PhD](#), and [Deanne Taylor, PhD](#), the new Center will position the Research Institute at the forefront of this fast-evolving research area.

Drs. Tan and Taylor see many opportunities for the CSCB to foster new collaboration and generate multidimensional insights within the Research Institute’s scientific community. They look forward to partnering with Biobanking and Pathology to develop clear and efficient protocols for tissue acquisition that support availability of high quality single-cell-ready samples. Another natural partnership is with the Arcus team, who are leading an enterprise-wide effort to centralize CHOP data from all areas of clinical care and research, to create a single cell data repository that ranges from omics to imaging data.



The image shows a large, detailed bronze dragon sculpture in the foreground, its head turned towards the left. In the background, a multi-story building with 'Drexel' signage is visible under a blue sky with some clouds. The text 'Drexel University Alliance Creating Opportunities' is overlaid on the left side of the image.

## Drexel University Alliance Creating Opportunities

By pairing-up some of the brightest scientific minds in the city and adding a fast-paced, rigorous academic environment, CHOP and Drexel University are well equipped with the knowledge and skills needed to advance pediatric medicine in pioneering ways — locally and internationally.

The new [Drexel University alliance](#) is creating opportunities for joint research activities among non-clinical investigators at both institutions, while enhancing educational programs at Drexel that include adding training opportunities for Drexel doctoral and master's students at CHOP.

Eligible non-clinical research scientists at CHOP will be offered non-tenured research track appointments as CHOP-based Drexel research faculty at the College of Computing and Informatics; Dornsife School of Public Health; or the School of Biomedical Engineering, Science, and Health Systems. As CHOP employees, the research faculty will be located primarily at CHOP, but will engage with Drexel students, staff, and faculty in their research efforts and become part of Drexel's academic ecosystem.

The alliance extends through June 30, 2023.

*Photo Courtesy of Drexel University*

## Innovation Ecosystem Bridges Silos



### INS AND OUTS OF ENTREPRENEURSHIP

**"We have unbelievably experienced people — who actually all love to mentor and teach — contributing to this resource, which is really incredible."**

tools and practices with individuals, groups, and departments. Think of it as the "amniotic fluid" — surrounding, connecting, and supporting — the hubs of innovation across CHOP.

This cross-functional team led by [Flaura Winston, MD, PhD](#), empowers people by exploring optimal ways to build individual and institutional capacity in the discipline of innovation, bridging silos to build multi-disciplinary innovation teams, and connecting those with identified problems with the people and resources needed to create innovative solutions.

"Our job is to overcome challenges, bring people together, and be the glue where people can share across these different groups," Dr. Winston said. "People at CHOP are our most valued — and valuable — asset and they are the people who come up with the future of what clinical practice and community activities should look like to benefit children. We need to make sure that we hear those ideas from these bright people."

This has been a busy year for our [Innovation Ecosystem](#) team, as they aim to help innovators — and innovative ideas — move through CHOP further and faster by facilitating cohesion among CHOP's innovation hubs. Just three years young and still growing, the Innovation Ecosystem serves as the connecting infrastructure across CHOP that identifies and improves innovation pathways and develops innovation



## Arcus Team Partners With Researchers and Families

### FORWARD THINKING

"These collaborative efforts are hugely important."

officer, is providing investigators with access to data from the CHOP enterprise as well as data analysis tools.

As a prime example of Arcus at work, researchers and co-leaders of the [Pediatric Sepsis Program](#), [Scott Weiss, MD, MSCE](#), and [Fran Balamuth, MD, PhD](#), teamed up with Arcus data scientists, to validate a pediatric surveillance algorithm relying on eight years of routine clinical data within CHOP's electronic health record as a dependable way to identify trends in pediatric sepsis.

By engaging and collaborating with CHOP's [Family Partners](#), the Arcus team is motivated to keep improving. In focus groups and team meetings, these families shared their personal journeys, concerns, and opinions about the use of their child's information in the Arcus archive. And when the pandemic and mandatory shutdown of our research labs hit in March, the [Arcus Education team](#) responded swiftly and creatively by introducing an ambitious schedule of live, online training dealing with a variety of data science topics.

"The most challenging problems in child health require the most sophisticated data and computational approaches," Pennington said. "Children's health is dynamic and families understand that CHOP will make breakthroughs in child health when we link data and use data science in a responsible way. Arcus is partnering with families to make responsible progress."

CHOP research teams are taking advantage of access to this dynamic data library and the expertise of Arcus data scientists, analysts, and archivists. With more than 30 scientific projects underway, [Arcus](#), under the leadership of [Jeff Pennington](#), associate vice president and chief research informatics

# A Research Community Comes Together to Fight COVID-19



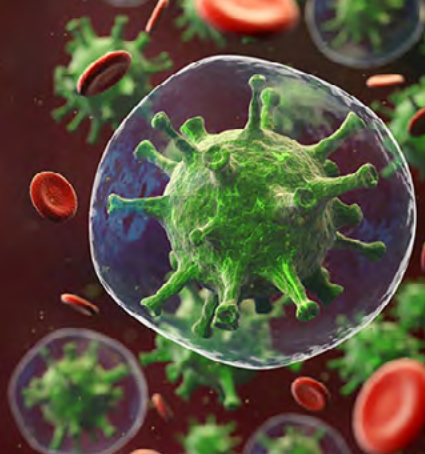
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When the COVID-19 pandemic began, the Research Institute quickly pivoted to focus on fighting the novel coronavirus.

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- 38**    Tracking and Tracing SARS CoV-2
- 39**    Working Toward a Treatment
- 40**    COVID-19 in Children: Challenging What We Know
- 41**    Caring for the Community in a Pandemic

## Tracking and Tracing SARS CoV-2



Researchers at CHOP moved quickly to develop methods of tracking SARS CoV-2, the virus that causes COVID-19, as it spread across the nation, through our local community, and within the human body itself. [David Rubin, MD, MSCE](#), director of [PolicyLab](#), and an interdisciplinary team at CHOP created a [modeling tool](#) using data from 819 U.S. counties to help state and local officials determine appropriate social distancing measures. The team shared their insights across local and national media, from guidance for in-person learning to [predicting transmission waves in areas across the country](#).

### MUCH TO LEARN

"We hope this study will help others outside of CHOP learn more about how a workforce at a pediatric institution may be exposed to this virus."

Closer to home, [Brian Fisher, DO, MPH, MSCE](#), physician in the Division of Infectious Diseases, and co-investigator [Jeffrey Gerber, MD, PhD](#), associate chief clinical research officer, [assessed immune responses to SARS CoV-2 among CHOP employees](#) to inform the best strategies for protecting our community. Through serology tests, they aimed to detect the number of people with symptomatic or asymptomatic infections and antibodies.

Meanwhile, [Audrey Odom-John, MD, PhD](#), chief of the Division of Infectious Diseases, enlisted the help of [working dogs to develop a novel way for detecting COVID-19](#) by tracking olfactory traces it may leave in the breath. Working with the Penn Vet Working Dog Center, Dr. John, who conducts similar research in malaria, aimed to identify the biomarkers needed to develop a "breathalyzer" test for COVID-19. Dr. John is also [tracing the concordance of SARS CoV-2 in the upper and lower respiratory tracts](#) to determine whether a patient might receive a negative result in current standard COVID tests but still have the virus present in their lungs or lower tract — insights that could help healthcare providers protect themselves and others.





## Working Toward a Treatment

As some CHOP researchers trace COVID-19's reach, other scientists are working toward treatments using a variety of approaches. In the lab of [John Maris, MD](#), physician in the Division of Oncology, researchers adapted computational tools to [identify the regions, or epitopes, of SARS CoV-2 to focus on when developing a safe, effective vaccine](#). The team identified 65 peptide sequences to prioritize for vaccine development, publishing their work in [Cell Reports Medicine](#).

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### VACCINE ROADMAP

"We looked at unique aspects of SARS-CoV-2 that make it so infectious and deadly, including its ferocity in attaching to lung cells, to determine which unique vulnerabilities we could target with a vaccine."

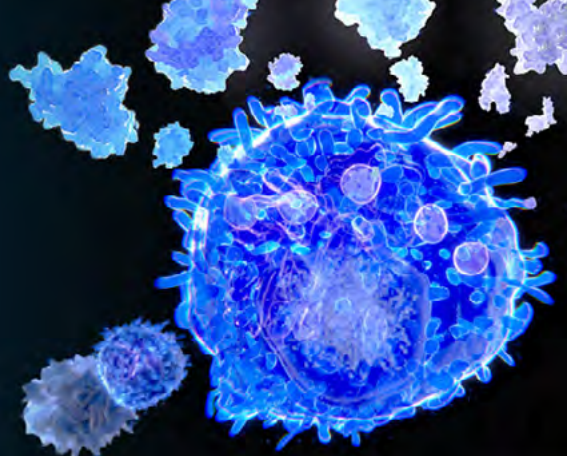
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Meanwhile, [David Teachey, MD](#), co-leader of the [Immune Dysregulation Frontier Program](#), and colleagues explored [the use of convalescent plasma, taken from recovered patients, to treat critically ill COVID-19 patients](#). Alongside a host of other departments at CHOP and the University of Pennsylvania, Dr. Teachey also began studying why, with some exceptions, pediatric patients seem to fare better in recovery than adults.

The team opened a protocol to collect blood from consenting patients with COVID-19 for comparison with adult patients.

Working in the lab of [Ophir Shalem, PhD](#), trainee Stephanie Sansbury began to adapt the CRISPR-based genetic screens typically used to study neurodegenerative diseases to learn more about COVID-19's pathology. Sansbury aims to identify a list of genes necessary to produce two proteins that SARS CoV-2 grasps onto to enter a cell. Her goals are to produce recommendations for which genes to target with drugs and to better understanding how the proteins are regulated.

## COVID-19 in Children: Challenging What We Know



Harnessing their expertise in children's health, researchers at CHOP sought to explore how the virus specifically affects pediatric patients. [Susan Coffin, MD, MPH](#), associate chief of Infectious Diseases, began a [natural history study that aims to understand the course of COVID-19 in children and why they seem to be largely spared from severe illness](#). Using information collected within CHOP's pediatric care network and with plans to partner with other U.S. children's hospitals, Dr. Coffin's team will analyze the data on a rolling basis and study how many diagnoses are being made, how frequently diagnoses are being made, and how children are presenting with the disease.

Meanwhile, a multidisciplinary team of researchers are [unraveling the mysteries of multisystem inflammatory disease \(MIS-C\)](#) that affects some children after coronavirus infection. [Katie Chiotos, MD](#), a physician in Critical Care Medicine, published a study of six children with MIS-C at CHOP, describing the cases as "a type of immune-mediated phenomenon" and COVID-19 that did not appear in a way they recognized. Building on Dr. Chiotos' data, research led by [Ed Behrens, MD](#), chief of the Division of Rheumatology, reported that children with MIS-C harbored high levels of two particular cytokines, TNF-alpha and IL-10, compared to children with a severe SARS CoV-2 infection.

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### PATHWAYS OF DISCOVERY

"If we can understand what's uniquely happening in children's immune systems and how they respond to COVID-19, then maybe we can figure out why adults are getting so sick."

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Dr. Behrens also is studying [what role cytokine storms, an overzealous immune reaction, may play in some severe cases of COVID-19](#). By completely characterizing the immune landscape of children infected with COVID-19 — from looking at the kind of antibody response children make to the cytokines they produce — Dr. Behrens hopes to learn something new about what makes people sick that might lead to better therapies or earlier diagnoses.

## Caring for the Community in a Pandemic



### THINKING CRITICALLY

"Knowing that Philadelphia and Pennsylvania have disproportionality in the ways in which COVID-19 has been impacting African-American, Latinx, and some immigrant communities, this is an opportunity for us to help..."

resilience factors (such as self-reliance) on mental health and sleep during the pandemic. "We expect the results to shed light on how and why some people manage to overcome adversity, while others struggle and develop stress-related disorders," Dr. Barzilay said.

Alongside Penn colleagues within LiBI, [Wanjiku Njoroge, MD](#), psychiatrist at CHOP, is [studying the challenges faced by Black women living in Philadelphia amidst two pandemics](#) (COVID-19 and structural racism), and the ways in which interventions could be helpful. Dr. Njoroge's study surveys postpartum mental health, physician trust, perceived discrimination, and other factors in peripartum women during the pandemic, aiming to create nuanced, supportive, and culturally appropriate care models.

[Christopher Forrest, MD, PhD](#), director of the Center for Applied Clinical Research, is also leading an effort to help the wider community adapt to the "new normal" brought on by the COVID-19 pandemic. As part of a wider network of institutions, Dr. Forrest is CHOP's leader in the Healthcare Worker Exposure Response and Outcomes (HERO) Registry, [which seeks to understand the needs and concerns of healthcare workers during the pandemic](#).

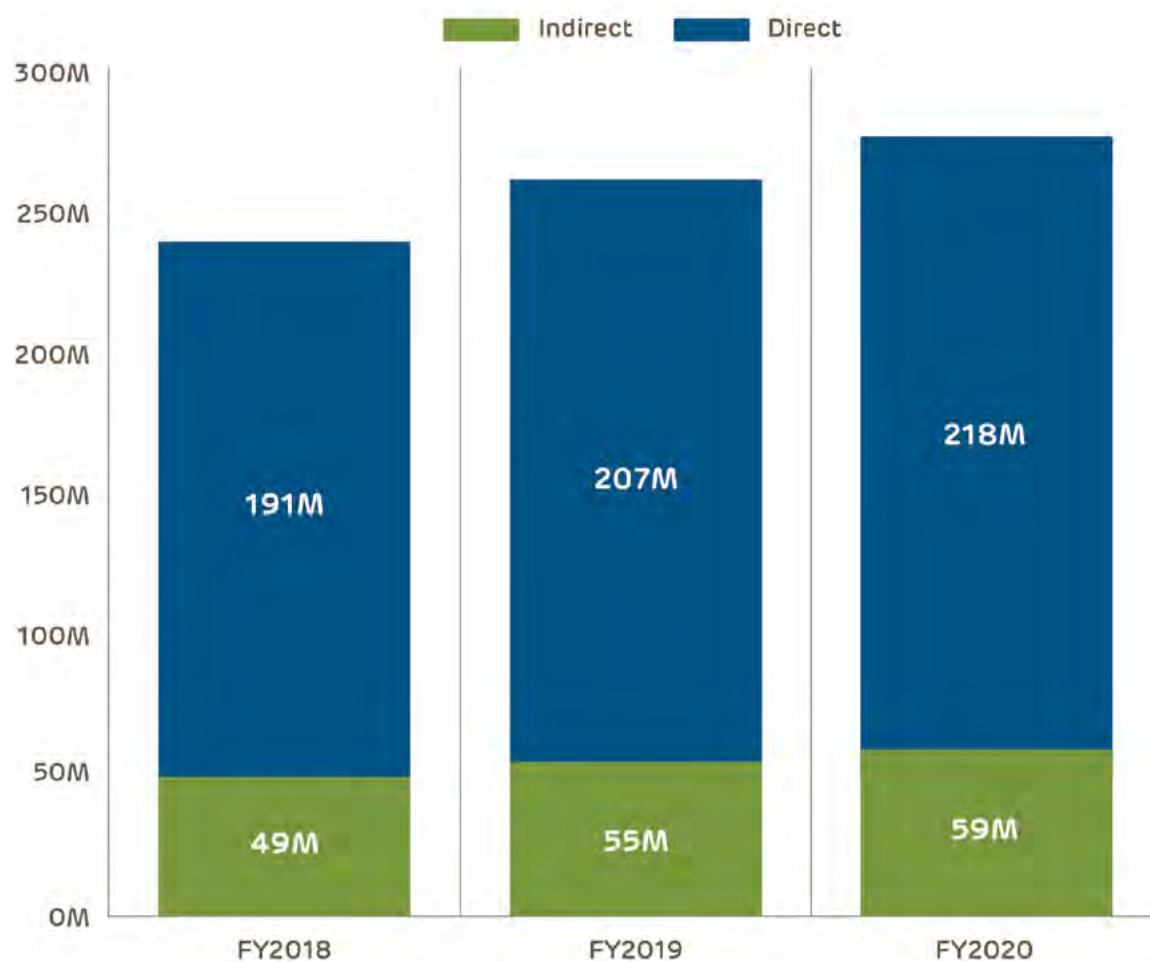
"This is a community that stands ready and willing to be involved in studies that can help address their needs during this pandemic," said Dr. Forrest of the HERO Registry. "We're in COVID time now, and we need to be ready. I want tools to help healthcare workers available in weeks not years."

Alongside the clinical impact of COVID-19, CHOP researchers also addressed the mental effects of the pandemic and the virus. A team at the [Lifespan Brain Institute](#) (LiBI) including psychiatrist [Ran Barzilay, MD, PhD](#), sought to study how to help individuals exercise resilience in challenging times. The researchers [developed a 10-minute online survey to be used as a research tool](#) that investigates the moderating effect of risk factors (such as negative relationships) and

# 2020 RI Annual Report Facts and Figures

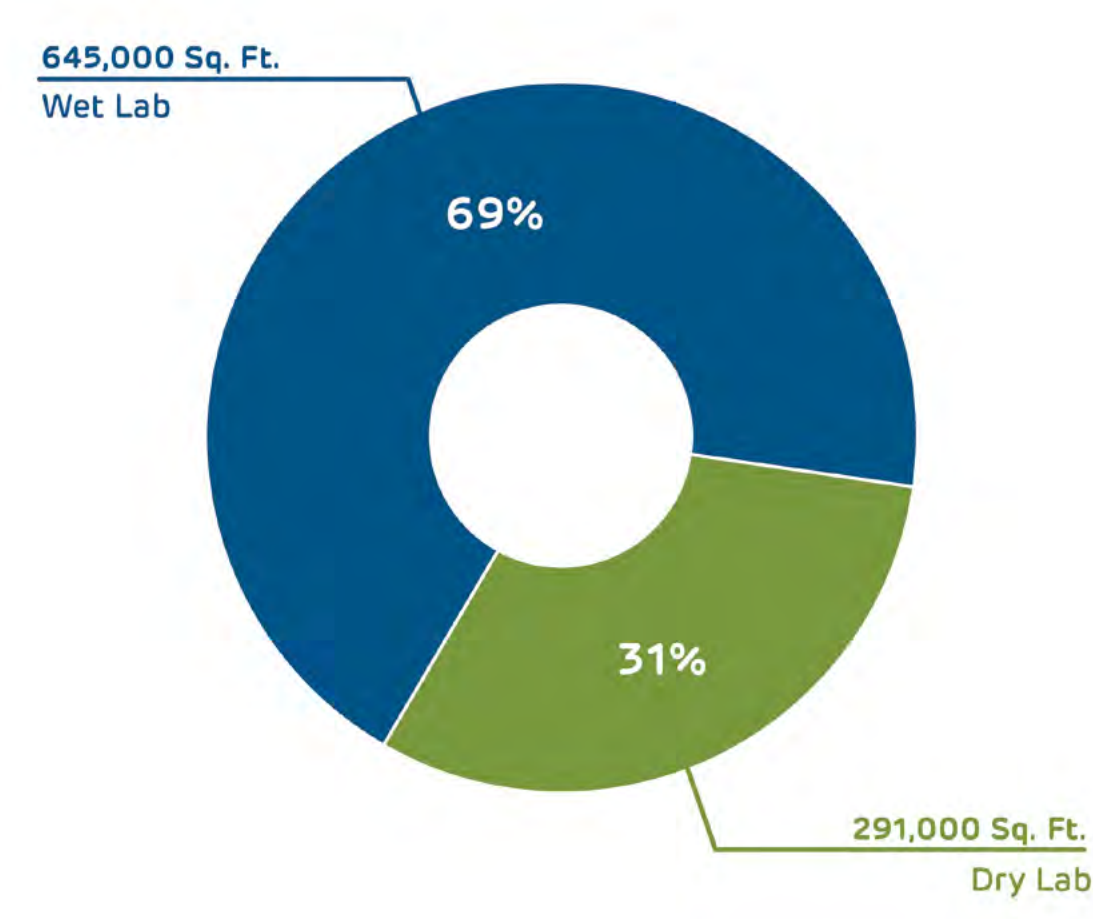
## Key Metrics

### Total Grant Funding

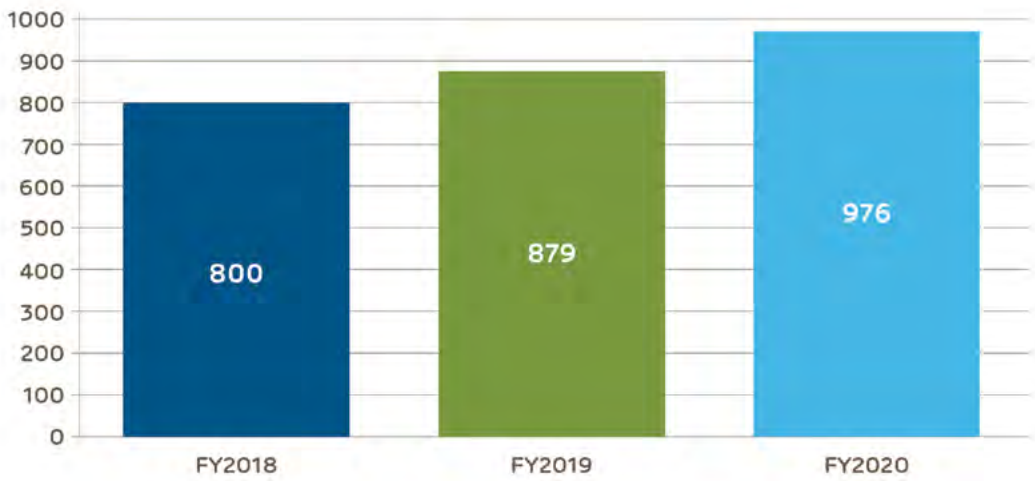


FY20 Research Space (Sq. Ft.)

Total: 936K



Number of PI (With Active Grants/Protocols)



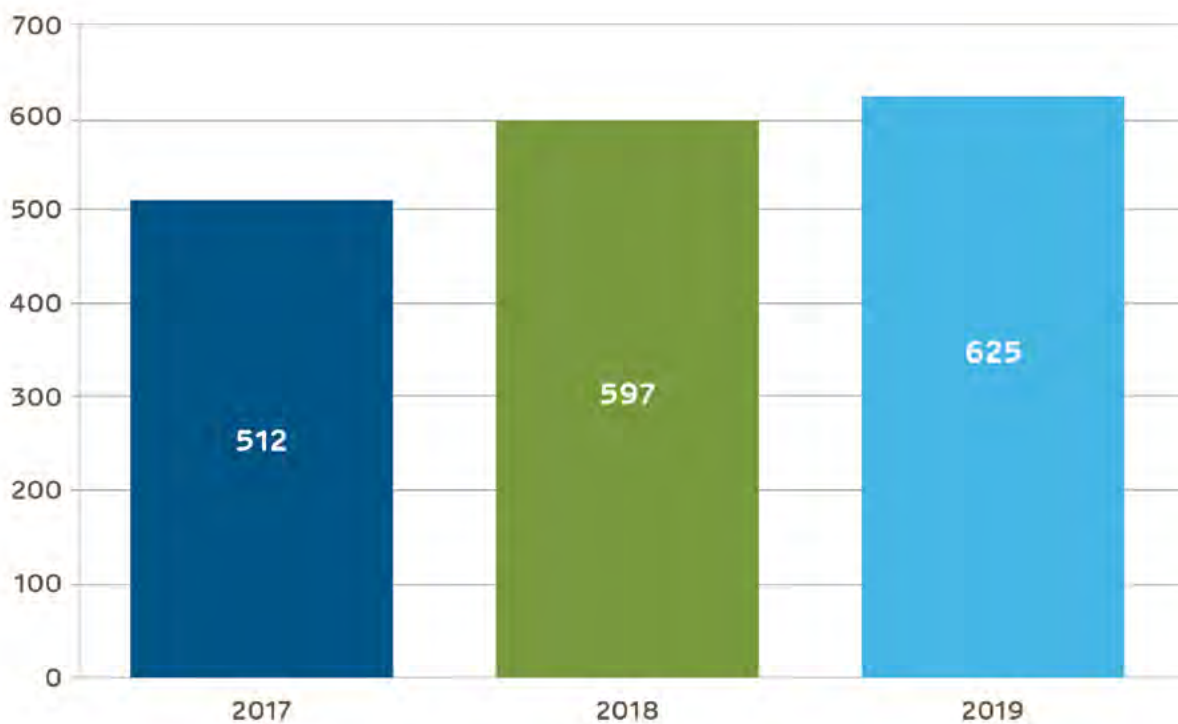


## Wet Lab - Average \$/Sq. Ft.

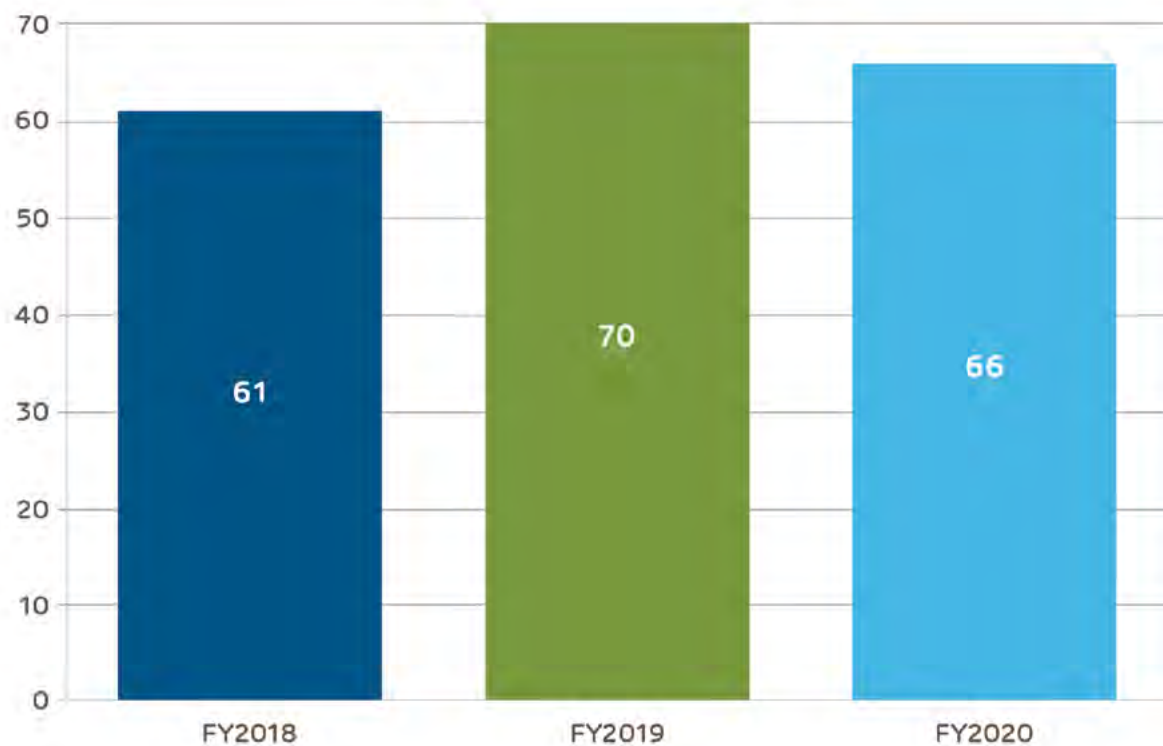


## Strategic Impact & Innovation

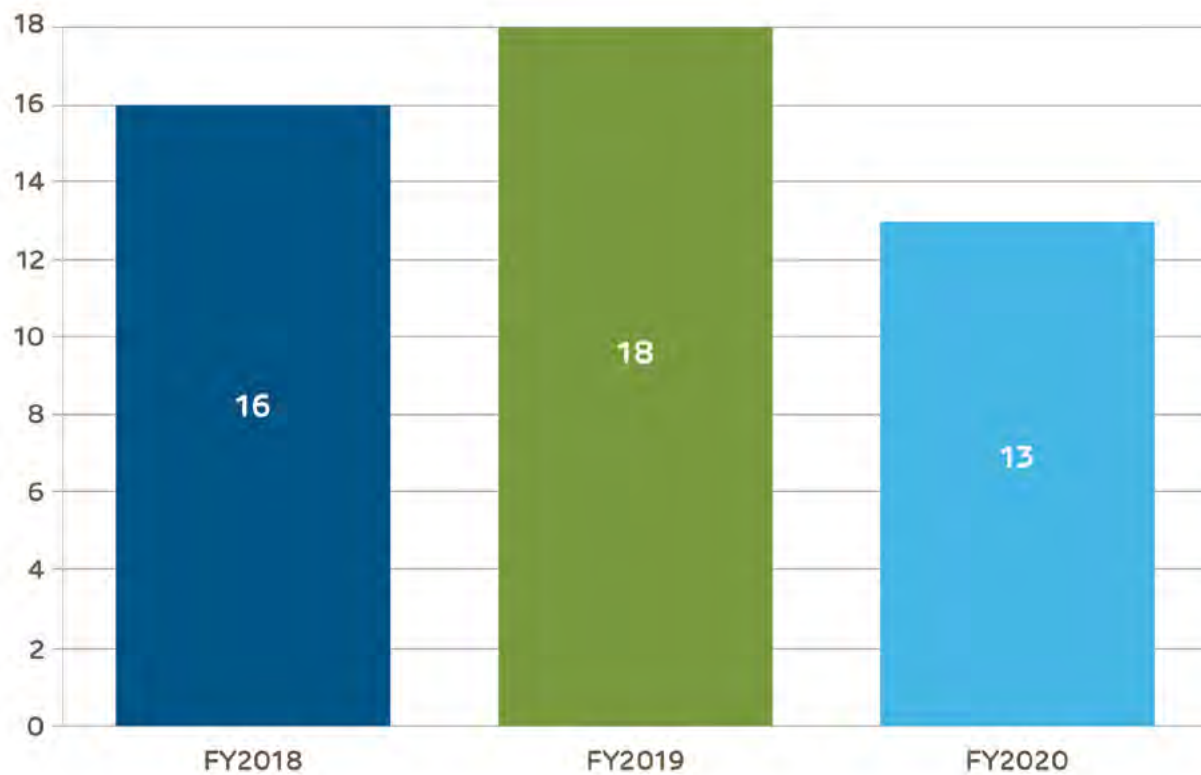
### Number of High-Impact Publications (Calendar Year)



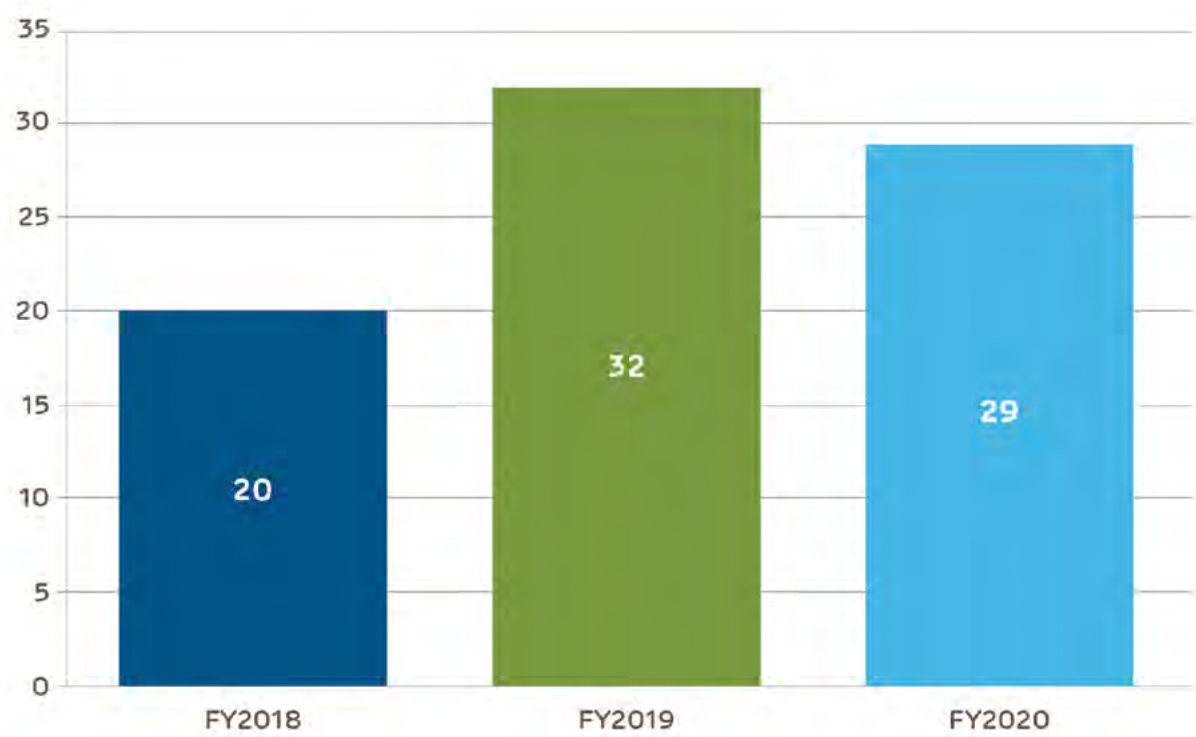
## Number of New Patent Applications



## Number of Patents Issued



## Number of Licenses & Options



## Key Strategic Initiatives & Growth

