INSTITUTE FOR PRECISION MEDICINE

A partnership of the University of Pittsburgh and UPMC

INTRODUCTION

THE INSTITUTE FOR PRECISION MEDICINE (IPM) is a collaboration between the University of Pittsburgh and UPMC that facilitates movement of biomedical research into personalized clinical care. The over-arching goal is to help researchers and clinicians discover and exploit clinically actionable information concerning the risk of disease, disease course, and optimal treatment/response.

This report details activities and outcomes of the IPM for 2019 and 2020. During that time the IPM has continued to promote and implement precision medicine at Pitt and UPMC. The IPM collaborates with many other departments, centers, and institutes across Pitt and UPMC to ensure rapid progression of precision medicine research.

During 2019 and 2020 the IPM has received funding support from UPMC and has successfully attracted grant support from the Richard King Mellon ($2.9M) and Leon Lowenstein ($250,000) Foundations.

Vision and Goals

The University of Pittsburgh and UPMC will lead the nation in precision medicine research and its application to personalized well-being and care.

- Enable and foster collaborative research
- Move research to personalized well-being and clinical care
- Raise understanding of precision medicine through education and awareness of personalized care at UPMC

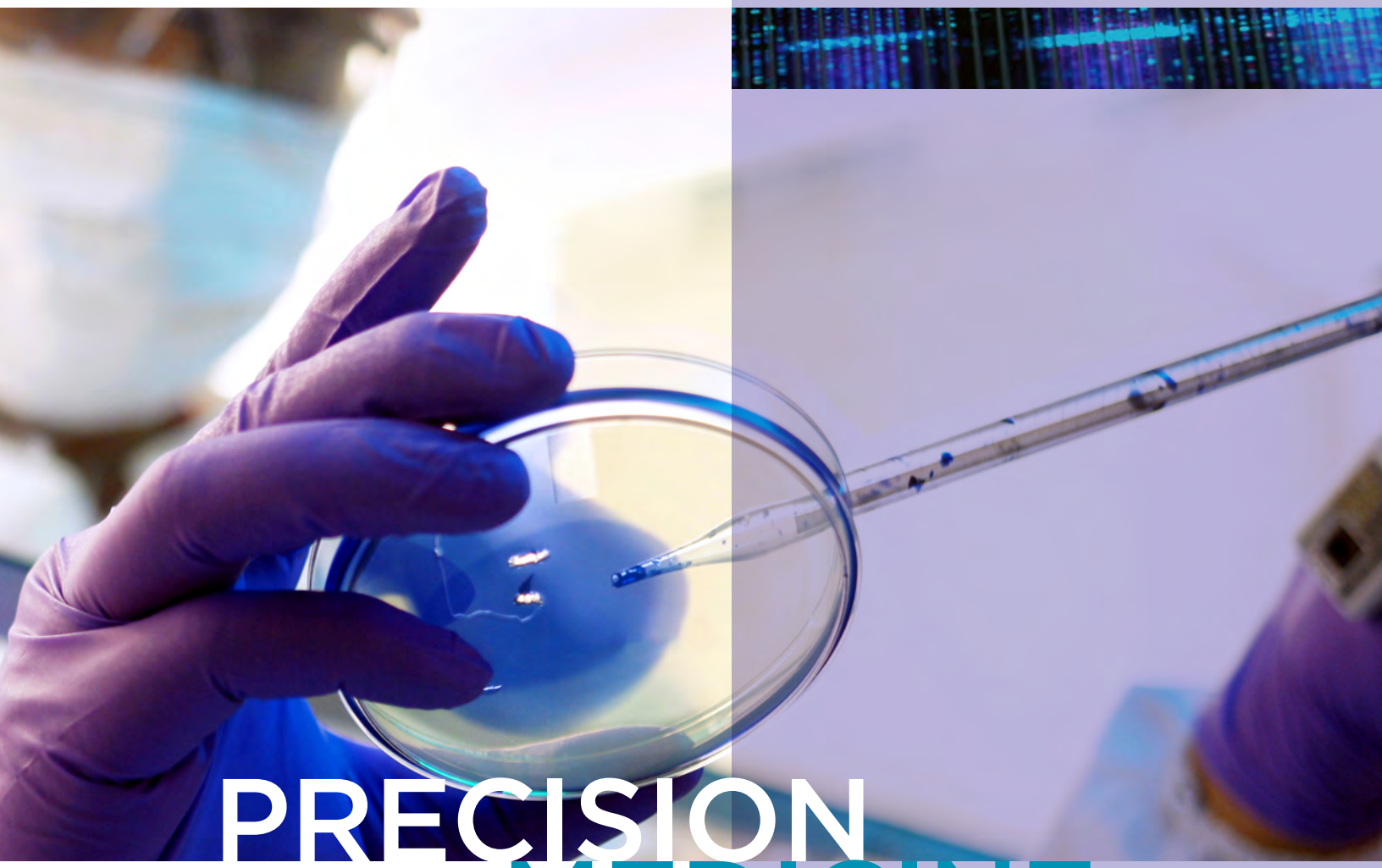
Focus Areas

Precision Biobanking

Genomics and Data Analytics

Education and Outreach

Implementation Science



PRECISION MEDICINE

RESEARCH INVESTMENTS AND ACHIEVEMENTS

Over the past two years, many significant achievements occurred related to precision medicine, some directly funded and driven by the IPM and some involving indirect interaction and support.

IPM-FUNDED INITIATIVES AND ACCOMPLISHMENTS 2019 AND 2020

PRECISION BIOBANKING

- Enhanced Pitt Biospecimen Core by full linkage to the UPMC electronic health record to enable clinical annotation of samples and research specimen selection
- Established an organoid resource living biobank for development, characterization, and sharing of organoid models for translational cancer research
- Implemented a revised University of Pittsburgh Tissue Use Policy to enhance collaboration with academia and industry
- Invested in infrastructure and equipment to increase productivity

GENOMICS AND BIG DATA ANALYTICS

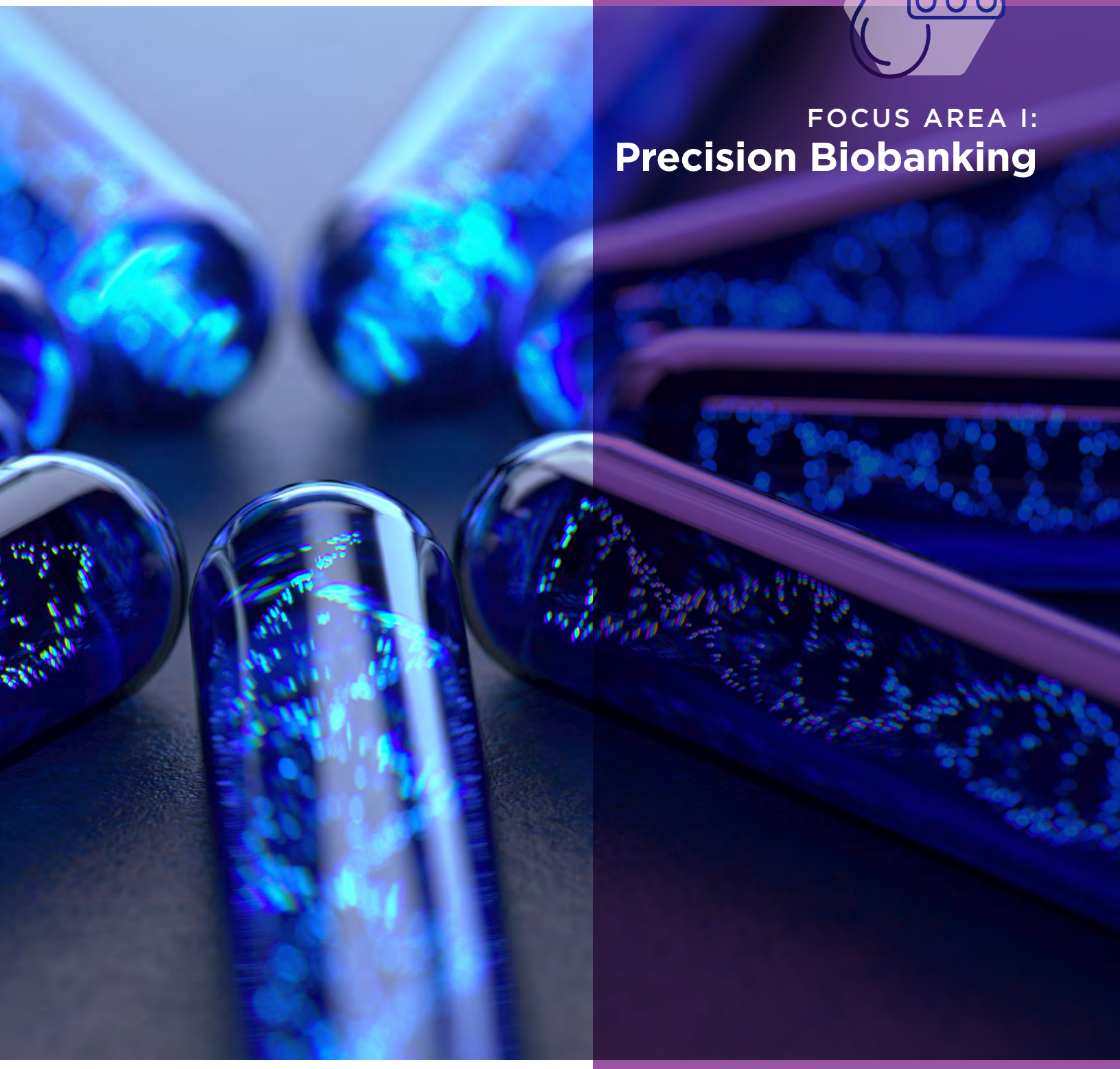
- Sponsored and promoted the use of genomics software, CLC Genomics Workbench, through the library which now has over 1,200 users and resulted in a 100-fold cost savings compared to individual licenses
- Promoted use of the UPMC Genome Center and Pitt Biospecimen Core through funding of 16 pilot grants
- Supported the Genomics Research Core in the purchase of a droplet digital PCR machine for unparalleled precision and absolute quantification of DNA copies for Pitt investigators
- Worked collaboratively across Pitt to apply for an S10 grant to update the high-performance computing cluster for health sciences researchers (scored 21, pending award notice)
- Received a $250,000 award from the Leon Lowenstein Foundation to support machine learning and artificial intelligence in sepsis (Critical Care Medicine)

EDUCATION AND OUTREACH

- Supported the expansion of the Test2Learn™ education platform into whole genome sequencing with funds from the Richard King Mellon Foundation
- Integrated Test2Learn for education about pharmacogenomics into the core Pitt School of Medicine curriculum
- Licensed to disseminate the Test2Learn platform to other universities to accelerate adoption of genomic medicine
- Performed IPM re-branding and developed a brochure and marketing materials highlighting IPM activities at Pitt and UPMC
- Performed successful outreach on the national stage through active participation (talks, booth) at the Precision Medicine World Conference in Silicon Valley in January 2020, talks at many national meetings (e.g. ASHG), collaboration on precision medicine meetings with the Center for Connected Medicine, and through mailing Institute for Precision Medicine brochures locally and nationally (targeted)
- Negotiated for the Precision Medicine World Conference to come to Pittsburgh, September 2021 (delayed from 2020 due to the COVID-19 pandemic)
- With the support from PittsciVelo of the Innovation Institute, the IPM implemented a commercial translation pilot program in Precision Medicine Commercialization (PreMIC) with funds from the Richard King Mellon Foundation
- Sponsored a regional Computational Medicine Conference in October 2019 focused on modeling approaches in biomedical research
- Philip Empey, PharmD, PhD, our associate director of pharmacogenomics, represented the IPM as a panel moderator at the Precision Medicine Leaders Summit in June 2019

IMPLEMENTATION SCIENCE

- Achieved IRB approval and implementation of in-house whole genome sequencing of critically ill babies in the neonatal intensive care units at UPMC Magee-Womens Hospital and UPMC Children's Hospital of Pittsburgh with support from the Richard King Mellon Foundation
- Expansion of the Primary Care Precision Medicine Clinic volume and service and funding for clinical sequencing through the UPMC Genome Center
- Validated new clinical pharmacogenomic testing and genotyped >6,000 patients at the UPMC Genome Center for pharmacogenomic variants with clinical decision support for return of results under development



FOCUS AREA I:

Precision Biobanking

There is critical need and demand for well-annotated biospecimens to fuel precision medicine as reflected by the growing size of the global market and the importance of biospecimens in all phases of therapeutic and diagnostic development. These can, and should, be developed in partnership with the biotech industry and pharmaceutical companies.

The IPM facilitates the largest biobanking effort at Pitt/UPMC through the Pitt Biospecimen Core (PBC). The PBC provides central support for research programs needing tissue materials for research and is key to the success of research in precision medicine, though it is just one of many biorepositories on campus.

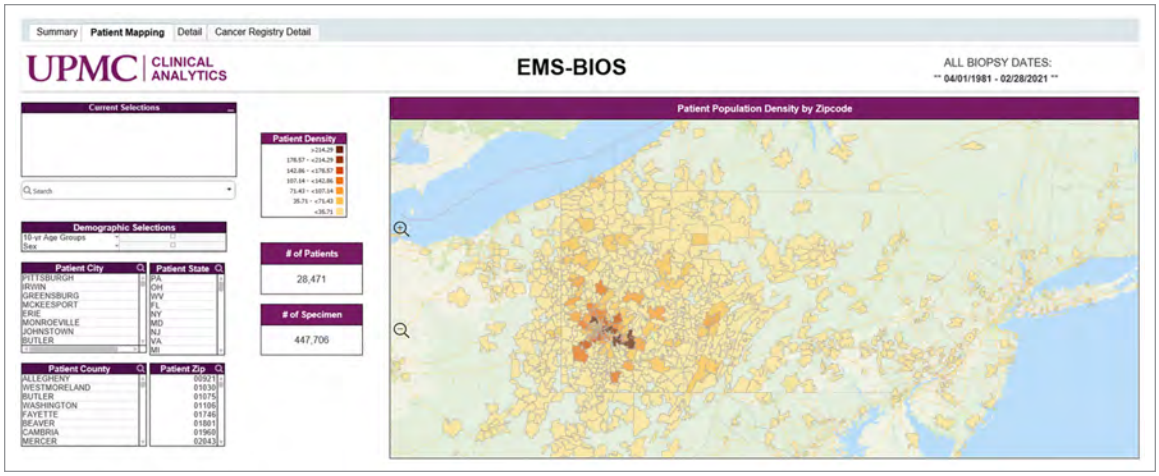
The PBC contains over 800,000 biological samples from about 65,000 patient visits to UPMC hospitals over the past 25 years. These samples are frozen surgical excess tissue and biofluid specimens from cancer, other disease states, normal and marginal tissues, as well as control individuals such as family members. In order to ensure biobank sustainability and ability to support the changing needs of researchers a number of initiatives occurred over the past two years. In 2019 alone the PBC organized and implemented >22,000 fluid and >6,000 solid tissue collections for investigator requests and disbursed >5,000 frozen samples and >1,800 fresh tissues.

A. GROWTH OF PBC

In order to support the varied needs of researchers across campus, the PBC has expanded services at some locations. Expanded services include access to fresh tissues and a pilot for 'out of hours' sample collections for increased flexibility of the PBC to meet the needs of researchers. Surveys conducted by core users identified project administration bottlenecks and a second project manager was added to the team in 2020. They also added a third histology technician and an assistant in 2020, and an older-model tissue stainer was replaced to keep up with productivity needs. Further, the PBC is in the process of launching an additional site at UPMC Children's Hospital of Pittsburgh. Renovations are complete and laboratory setup and stocking are in the final stages; onsite collections are expected to start by July 2021.

B. CONNECTION OF PBC SAMPLES TO THE ELECTRONIC HEALTH RECORD

A major weakness of tissue banks around the country is that they aren't directly linked to clinical information due to de-identification for research. The PBC is unusual in that the staff are all honest brokers and the database and all PBC computers and communications sit on the UPMC network. This allows all samples to remain fully identified in a UPMC-built database called the Biospecimen Inventory and Operating System (BIOS). We identified an opportunity to link BIOS to the data warehouse generated by Oscar Marroquin, MD, FACC, UPMC's chief health care data and analytics officer, and funded this linkage. In cooperation with the UPMC BIOS developer, Avinash Vemulapalli, and Kevin Quinn from Dr. Marroquin's team, the PBC systems analyst and compliance team completed the linkages required for automated uploads of data from the PBC to the UPMC data warehouse. Due consideration was given to assure that data are queried and reported in a regulatory compliant manner. A working dashboard has been created that allows for any field from the patient record and BIOS record to be used to filter available samples. These queries can be used to assemble the most appropriate sample set to achieve a given research goal and provide valuable metadata as part of a standard or custom report. The PBC systems analyst, Phillip Schumacher, has been trained to access all the combined EHR and BIOS data and run queries and reports to identify samples found within the PBC based on these combined fields. The UPMC clinical analytics team is very responsive to add fields and capabilities based on the needs of PBC investigators. The PBC is exploring a transition from BIOS to the new dashboard for most or all queries and reports. This would provide utility beyond the initial expectation of using it to provide specialty reports and would allow maximum value of the EMR linkages achieved through this effort. The dashboard linkage is in regular use and has allowed for investigators to obtain valuable metadata related to the samples that they collect, store, and distribute via the PBC. This includes any lab or diagnosis and other criteria such as ZIP code.



Screenshot of electronic medical record and biobank searchable interface.

In the future, the system may also enable investigators to gain a restricted data view and perform their own exploration of PBC samples and related EMR fields. We hope to use this ease of access to associated clinical data as a promotion of the biobank to internal researchers as well as outside companies to stimulate collaboration.

C. VIRTUAL BIOBANKING CAPABILITIES

In addition to the PBC resource, there are numerous other biobanks across Pitt. In order to catalogue these biorepositories with aggregate level data, the IPM has been working closely with Paul Wood, assistant director for core facilities office of research health sciences, to identify all biospecimen resources. A catalogue of repositories will be of significant value for researchers seeking research specimens who will be able to contact the repository guardian for further sample-level data. The goal in establishing this database was to maximize the utility of samples already collected by providing investigators with the samples that they need without having to resort to unnecessary collection of additional biospecimens. With input from faculty investigators and in cooperation with pathologists, data specialists from the Health Sciences Library System, and Jonathan Silverstein, MD, MS, FACS, FACMI, from the Pitt Department of Biomedical Informatics (DBMI), a data collection survey was constructed and implemented within Redhat (https://is.gd/PittBiorepositoryDatabase). The resulting Pitt Biospecimen Database (PBD) is actively curated and has been widely distributed. Development of a searchable web application was completed by a team at the DBMI and is currently available in the UPMC and Pitt domains to search the available data (pbd.pitt.edu). This application allows an investigator to search for collections of samples that meet specified criteria and to review pertinent information about those collections. It contains the information that will enable contact with the principal investigator (PI) of a biorepository in order to explore whether or not access to the samples is possible and collaboration is of mutual interest. The completion of the PBD data collection survey is now mandatory for distribution of samples outside the University, which has driven the data collection process and appears as a prompt in MyRA to enter the PBD number of the collection samples belong to. As the new Health Sciences Tissue Governance Policy is rolled out and advertised (Jennifer Xavier, PhD, the IPM's associate director of research, served on the policy review committee), all Health Sciences faculty have been, and will be, encouraged to input data for their biorepositories. The end goal is the creation of a universal, searchable bio sample database linked with clinical information for access by the entire university community to enhance research collaboration and translational research.

D. DEVELOPMENT OF ADVANCED TECHNIQUES – 3D ORGANOID CULTURES

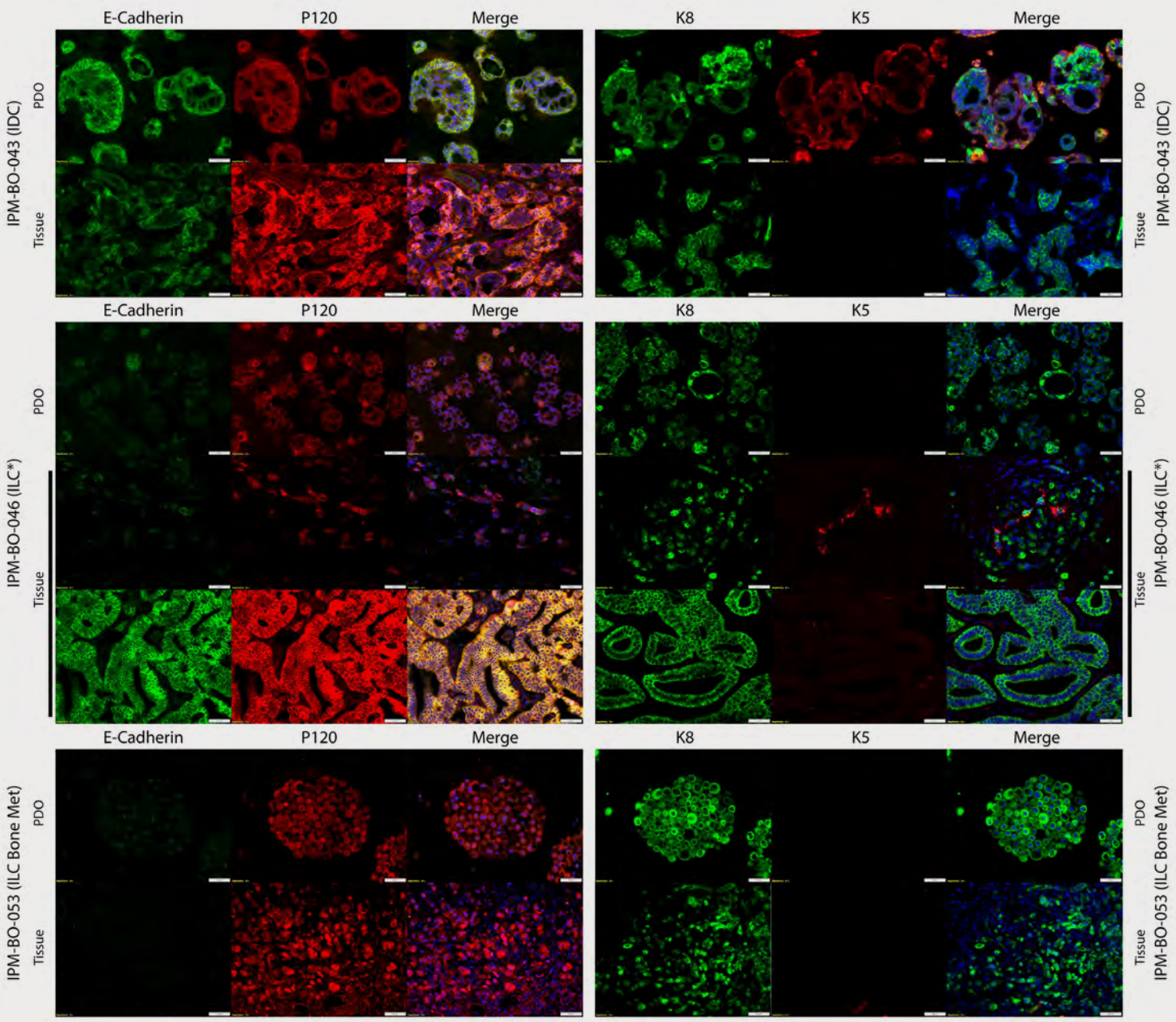
The PBC has adapted over time; for example, most investigators now request fresh tissue instead of frozen. At the forefront of the development of more sophisticated in vitro models in which to study disease are advanced three-dimensional culture methods to expand and study cultures from patient tissues. Multiple studies have shown that 3D culture models such as patient-derived organoids are often superior to traditional 2D culture methods in the recapitulation of patient disease pathology, heterogeneity, and response to drug treatment, paving the way for potential critical advances in precision medicine. To advance the development of methods for creating patient-derived 3D models from multiple disease types, and to develop a 'living biobank' of organoid models for Pitt researchers, the IPM hired a research scientist, Daniel Brown, PhD, on July 1, 2018. Our goal is to successfully culture, expand, and cryopreserve living tissue-derived organoids to be used for research of multiple disease types. The growth and behavior of the developed organoid models are being compared to the pathology and outcomes in the patient lesions and to established 2D cell line models. To date we have established 49 organoids from a total of 60 breast tumor samples received from patients undergoing resection of their primary or metastatic breast tumor, resulting in a success rate of 82%. Our organoids demonstrate a range of growth morphologies, consistent with those previously described. We have demonstrated that organoids are amenable to transient transfection of siRNA and lentiviral infection of reporter constructs which allows for RFP and luciferase-based detection of cells both in vitro and in vivo as well as expression of genes of interest. Single cell RNA sequencing (10X Genomics) of organoid cultures and paired tumor tissue confirmed that organoid cultures faithfully maintain the heterogeneity of epithelial subpopulations found in the surgically resected tumors. As expected, the organoids show greater epithelial diversity and heterogeneity compared to single cell sequencing of breast cancer cell lines and we have further used sequencing data to identify targetable pathways in individual organoid cultures and demonstrate that drug sensitivity can be correlated with gene expression in these models. In the longer term, we plan to expand to further tumor types and to explore the possibility of organoid development as a fee-for-service opportunity for Pitt research groups accessible through PBC.

Patient derived breast cancer organoids retain histological features of the tumor tissue from which they are derived. Immunofluorescence images of tissues and paired organoids stained for specific cell type markers. PDO; patient derived organoid, IDC; invasive ductal carcinoma, ILC; invasive lobular carcinoma. K5/K6 Cytokeratin 5/6.

E. PILOT AWARDS TO STIMULATE USE OF PBC

We identified that a major barrier to use of the PBC was knowledge of what services and tissues were available. To stimulate use of the PBC, we issued a research funding announcement for investigators using banked tissues. We selected four applications to support the costs of retrieving 20 biospecimens:

- *The role of necroptosis and membrane damage in tumor microenvironments.* Yi-Nan Gong, PhD, Department of Immunology.
- *Spatial profiling of immune biomarkers in atypical breast lesions and breast cancer risk.* Phuong Mai, MD, Department of Obstetrics, Gynecology & Reproductive Sciences.
- *Comprehensive characterization of the mutational and transcriptional landscape of pleomorphic lobular invasive breast cancer (PLC).* Leisha Emens, MD, PhD, Department of Medicine.
- *E-cadherin and tight junction proteins are down-regulated in the aging prostate and associated with increased inflammation and disease pathogenesis.* Zhou Wang, PhD, Department of Urology.



FOCUS AREA II:

Genomic and Data Analytics

A. UPMC GENOME CENTER

A central component of precision medicine is the use of molecular features to better understand disease and predict risk and response to therapy. Genomics (DNA sequencing) is the current key feature being used to develop personalized disease models and enable personalized patient care. In April 2018, UPMC opened a state-of-the-art genome sequencing center which places Pittsburgh with capacity similar to or better than most of our competitors nationally. The UPMC Genome Center (UGC) (UPMCgenomecenter.com) is a world-class, clinical-grade, industrial-scale center with high-throughput sequencing capabilities.

The IPM plays a crucial scientific leadership role in the UGC. Specifically, we support sample collection and biobanking, enabling long-term access to research data. We anticipate that the UGC will create a "sea change" at Pitt/UPMC with many outsourced sequencing projects being possible in house, and due to the support of the UPMC Immune Transplant and Therapy Center, many investigators now have opportunities and financial support for sequencing large patient cohorts which was not possible before.

The UGC offers a multitude of services to the academic researchers at the University of Pittsburgh by offering help with study design and project planning, competitive pricing, timely sequencing, and bioinformatics processing. To date the UGC has sequenced over 10,000 samples and performed PharmacoScan™ on over 6,000 samples. The UGC has extended its customer base to over 100 different facilities or laboratories and over 200 investigators. The UGC has also contributed to the 2020 pandemic by sequencing COVID-19 samples for research purposes, including a study recently published in *Science* (PMID: 33154108).

B. STIMULATION OF UGC USE – PILOT AWARDS

To stimulate use of the UGC by Pitt researchers and to encourage them to try the UGC research services, we issued a research funding announcement for investigators interested in performing WGS. We selected 10 applications to support the costs of sequencing 16 human biospecimens per project:

- *Somatic Mutation Burden in Hypertrophic Cardiomyopathy.* Jason Becker, MD, Department of Medicine.
- *Clinical, Radiologic, and Molecular Characteristics of Anaplastic Pleomorphic Xanthoastrocytomas (WHO grade III).* Alberto Broniscer, MD, MS, Department of Pediatrics.
- *Toward Elucidating the Multi-Omics and Genome-Phenome Architecture of Pulmonary Hypertension.* Stephen Chan, MD, PhD, FAHA, Vascular Medicine Institute.
- *Whole Genome Sequencing to Explore Variability in Treprostinil Response in Patients with Pulmonary Arterial Hypertension.* James C. Coons, PharmD, FCCP, BCCP, School of Pharmacy.
- *Unanticipated Heterogeneity in PAH Deficient Phenylketonuria: Defining the Neuro-Refractory PKU Phenotype.* Steven Dobrowolski, PhD, Department of Pathology.
- *Comprehensive Characterization of the Mutational and Transcriptional Landscape of Pleomorphic Lobular Invasive Breast Cancer (PLC).* Leisha Emens, MD, PhD, Department of Medicine.
- *Whole Genome Sequencing to Identify Inborn Errors of Immunity in Neurologic Injury Following Viral Infection.* Kate Kernan, MD, Department of Critical Care Medicine.
- *Quantifying Genetic Variation in Postpartum Women for Pain and Depression.* Grace Lim, MD, MS, Department of Anesthesiology and Perioperative Medicine.
- *Personalizing Chemotherapy for Pediatric Liver Cancer.* Rakesh Sindhi, MD, Department of Surgery.
- *Whole Genome Sequencing for Treatment-resistant Multiple Sclerosis.* James Gilbert, PhD, Department of Plastic Surgery.

C. COMPUTATION

Biomedical researchers have an increasing ability to comprehensively interrogate cell and molecular biology, for example with advanced imaging and next-generation sequencing, but researchers face the challenge of larger and more complex datasets requiring advanced high-throughput computing (HTC). Before 2015, biomedical researchers had access to the Center for Research Computing (CRC) at Pitt but were computing alongside all other Pitt faculty with diverse applications. It was realized that some unique features of increased biomedical computing, such as memory-intensive and IO-intensive operations, may require an alternative approach. Recognizing the importance of data science in precision medicine, in 2015 the previous IPM director Jeremy Berg, PhD, and Pitt invested in a HTC cluster, with components specifically configured to address health science computational workflows. The HTC cluster is hosted in a secure and centralized enterprise-level data center and administered by the Pitt Center for Research Computing (CRC).

The HTC cluster (16 nodes with a total of 256 total CPU cores) was installed at the CRC. The HTC cluster was designated solely for biomedical researchers in the Schools of the Health Sciences. Usage of the HTC grew rapidly. In 2016, groups used 0.5M service unit (SU) usage (1SU = 1 core hour of computing). In 2017, this had grown to 1.3M SU. Last year (5/2019-5/2020), biomedical researchers used 3.1M SU. Thus, we have seen a 520% increase in usage over four years.

Consistent with the increase in use of compute hours on HTC, we also noted that the number of registered users has grown substantially since 2017. This growth is a testament to the need for biomedical computing and the ease of use of HTC, the scalable and secure environment, and the associated educational programs.

To enhance the computational infrastructure for precision medicine moving forward, we submitted an NIH S10 to upgrade HTC capabilities. We proposed a new HTC with 20 nodes with dual socket Intel® Xeon® Gold 24-core Ice Lake-SP processors (960 CPU cores). In addition, we have several biomedical researchers who require GPU and thus we will install two nodes with four high-end NVIDIA V100S GPUs in each for this growing area of research. This application received a score of 21 and we are awaiting a funding decision.

D. BIOINFORMATICS

Usage of the HTC cluster is provided without charge to all biomedical researchers at Pitt. User training for effective usage of the instrument is provided through a collaboration between the CRC and the Molecular Biology Information Service (MBIS) group within the Health Sciences Library System. The MBIS has several molecular biology PhD employees tasked with providing educational opportunities in genomics and bioinformatics. The CRC has a team of cross-disciplinary research faculties with expertise in computational algorithms and workflow methodologies. The many training opportunities offered are aimed towards lowering the barrier of using HTC paradigms by biomedical researchers. The dramatic rise in use of the HTC cluster (520% increased use over four years) is a testament to the effectiveness of this setup. This unique collaboration and the metrics of its success were recently described in detail in a publication.[1]

The growth of genomic sequencing has placed an incredible burden on bioinformatics support. The use of bioinformatics core personnel is key, however, this model is not sustainable and general lab researchers need to be educated to perform their own bioinformatics (at least simple low-level analyses). Towards this goal, the IPM has again supported the MBIS (Ansuman Chattopadhyay, PhD) of the Health Sciences Library System to financially aid the ongoing deployment of the CLC Genomics Workbench from QIAGEN. This software has a simple Windows user interface that can be readily used by wet lab researchers, and streamlines analysis of next generation sequencing (NGS) datasets such as RNA-Seq, Exome Sequencing, and ChIP-Seq. Given that (1) the analytical workflows for this software suite are complex and (2) the emphasis on rigor and reproducibility in data analysis is increasing, HSLS-MBIS collaborates with the Genomics Analysis Core of the Department of Biomedical Informatics (DBMI-GAC) to provide comprehensive assistance with the use of CLC Genomics Workbench for the analysis of NGS data. Through educational series, investigators are exposed to data preparation, data importation, and CLC Genomics Workbench software capabilities via an in-depth, three-hour monthly workshop offered by HSLS-MBIS. The CLC Genomics usage data (listed below) indicates continued and strong adoption of CLC software by the university research community.

This is in part due to the availability of the CLCbio Genomics Server hosted and maintained by the Center for Research Computing (CRC). A seamless integration with the CRC-high performance computing cluster allows users to run analysis on the cluster upon migrating the data from their workstation to the cluster. These software packages have 25-30 active users per day.

Number of Registered Users:

- ***CLC Genomics Workbench*: 1,208** registered users (as of **May 2020**); New Registrations: **312** (June 2019- May 2020, a **35%** increase over last year)
- ***Ingenuity Pathway Analysis*: 1,133** registered users (as of **May 2020**); New Registrations: **163** (June 2019- May 2020, **17%** increase last year). Total Hours Logged: 9,949; Sessions Logged: 8,335.

The average number of unique users per day for CLC Genomics Workbench totaled approximately 25 to 30. The increased use in April 2020 (see graph on opposite page) likely reflects increased bioinformatics research while wet research labs were shut down due to the COVID-19 pandemic.

Cost Savings:
The purchase of university-wide site licenses for Qiagen bioinformatics software provides an estimated ~100-fold reduced cost compared to individual licenses.

E. DATA ACCESSIBILITY AND SHARING

A central challenge in data analytics is access to data and efficient sharing for investigators. The mission of the Research Informatics Office (RIO), led by Jonathan Silverstein MD, MS, FACS, FACMI, and established in 2017, is to support investigators through innovative collection and use of biomedical data. Health Record Research Request (R3), established in 2018, is a signature program of the RIO, operated on behalf of UPMC through HIPAA BAA under UPMC policy HS-RS0005. R3 is a service of DBMI led by the CRIO, sponsored in part by the Clinical and Translational Sciences Institute (CTSI) and the IPM. Designated R3 staff of DBMI provision UPMC data for research (often as honest brokers). Both Pitt and UPMC use R3.

Objectives:

- Expand the capability and capacity for clinical data-driven research across Pitt via DBMI
- Provide intellectual input into the scope of work of non-DBMI led research projects
- Provide data services and informatics support to clinical and translational research
- Expand the research portfolio of Pitt and UPMC via collaborative projects

---

1) Chattopadhyay A, Iwema CL, Epstein BA, Lee AV, Levine AS. Molecular Biology Information Service: an innovative medical library-based bioinformatics support service for biomedical researchers. Brief Bioinform. 2020 May 21;21(3):876-884. doi: 10.1093/bib/bbz035. PMID: 30949666.

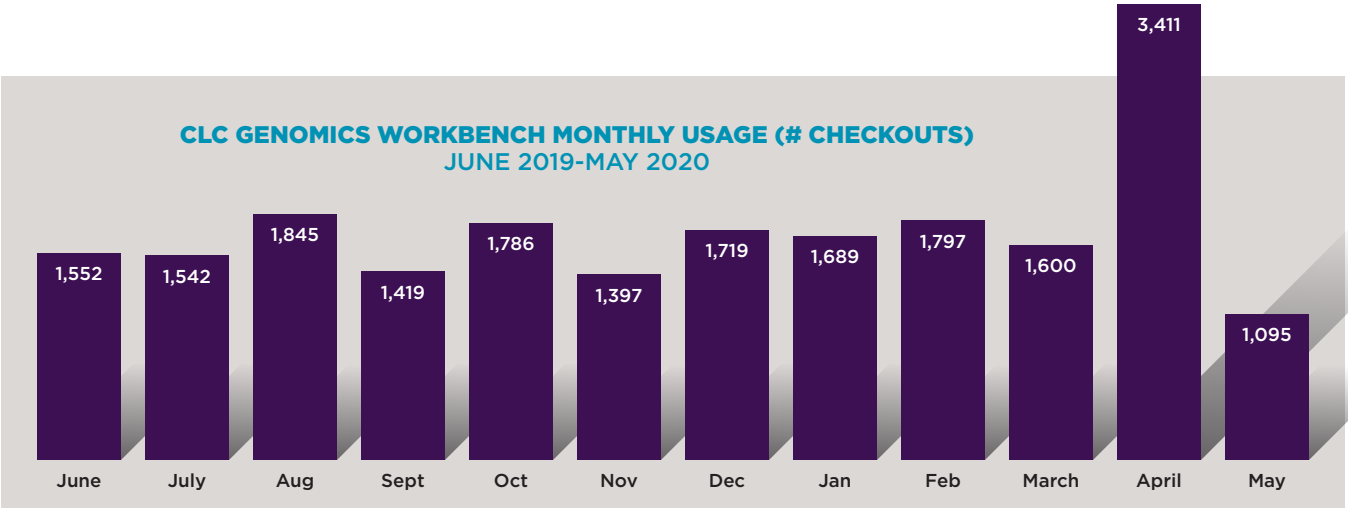


Figure: Unique users of HTC. *Graph showing the number of unique users per week of HTC over time. Note the slight decline in unique users from May to August 2020 likely due in part to COVID-19, but an increase since that time.*

Key R3 Achievements:

- Established policy and processes for R3: intake, specification, attestation, honest brokering, and delivery (UPMC audited and with oversight by CMIO)
- Developed a unique set of technologies and processes, performing at scale
- Neptune research data warehouse enables high volume, efficient, and secure extraction, linking, and de-identification of clinical data from numerous UPMC sources on ~4.8M patients
- R3 service recharge core facility receives ~900 intake queries per year with ~100 per year resulting in clinical data provisioned to investigators.
- Established base of collaborative informatics projects to infuse DBMI into other Pitt research
- Expanded data sources to include ~300 million clinical notes and ~2 Petabytes DICOM images

DBMI and CTSI are leading numerous national data-sharing projects such as Accrual to Clinical Trials (ACT) Cohort Discovery Tool. ACT is a web-based, multisite tool that helps researchers assess the availability of patient populations at academic medical centers across the United States via self-directed electronic health record searches. It helps with cohort discovery to determine study feasibility, study design, and identifying additional sites for a multisite clinical trial. It is envisioned that biomedical data sharing will continue to expand as a central requirement, and investigators in DBMI, CTSI, and IPM are well positioned to enable this.

F. ARTIFICIAL INTELLIGENCE AND SEPSIS

Through its ongoing relationship with the Leon Lowenstein Foundation, the IPM was able to support Critical Care Medicine (CCM; Chris Seymour, MD, MSc, and Derek Angus, MD, MPH, FRCP) in gaining $250,000 in funding support for understanding the use of artificial intelligence in the emergency care of sepsis. Using ML methods, the CCM group successfully derived and validated four novel clinical sepsis phenotypes at hospital presentation, now published in *JAMA* (PMID: 31104070). The grant from the Leon Lowenstein Foundation supports extending this knowledge by modeling the trajectory of sepsis phenotypes over the course of Emergency Department (ED) care. The goal is to deliver an individualized, optimal treatment strategy for patients with early sepsis by combining sepsis phenotyping with reinforcement learning modeling.

Grant aims include:

- *Applying machine learning (ML) to model sepsis phenotype trajectories.* Using variables measured during routine care, we identified four sepsis phenotypes at hospital presentation. We will employ similar ML strategies to model phenotypes over time using an existing data set of >1 million encounters. The benchmark of success will be a development of a matrix of sepsis phenotypes modeled across discrete time points to guide development of phenotype-specific treatments.
- *Leveraging reinforcement learning to deliver the best treatment strategy for individual sepsis patients.* We will apply ML to the phenotype matrix developed above and identify optimal phenotype-specific sepsis treatment. The benchmark of success will be delivery of an AI-powered optimal, individualized treatment algorithm to embed in the electronic health record in the form of a Substitutable Medical Apps, Reusable Technologies (SMART) app on Fast Healthcare Interoperability Resources (FHIR) for bedside deployment.

These results will serve as the basis for future work where the CCM team of bioinformatics and programmers will embed these scalable, phenotype-specific treatment algorithms in the electronic health record as a SMART app on FHIR for use at the bedside.

FOCUS AREA III:

Education and Outreach

A. GENOMICS EDUCATION AND TRAINING

Under the guidance of Dr. Philip Empey, the Test2Learn™ program, employing an awarding-winning participatory educational model using personal genomic testing, continues to expand nationally. In 2020, we developed a new learning platform and achieved milestones of training nearly >2,800 physicians, pharmacists, students, and other health care professionals and awarded >9,400 hours of continuing education through >74 online and live education programs deployments cumulatively.

Test2Learn™

Test2Learn (www.test2learn.org) is now integrated within the School of Pharmacy curriculum (since 2014) and the Pitt School of Medicine (since 2019). Our learning platform is currently freely licensed to 16 external universities and is foundational to our nationally deployed PGx certificate program with NACDS and 23andMe. Innovations include several invention disclosures, a novel micro-credentialing model, and industry collaborations. With grant funding awarded to the IPM from the Richard King Mellon Foundation, we are developing educational programs to advance whole genome testing awareness among clinicians and health system leaders. In 2020, we also received NHGRI funding to disseminate competency-based PGx education even more broadly and to integrate our local testing from the UPMC Genome Center into the platform. We expect that Test2Learn will be instrumental to our training of new practitioners, clinical champions, and the overall clinician workforce to accelerate precision medicine initiatives at UPMC. Beyond Test2Learn, Dr. Empey chairs the pharmaco-genomics group for NHGRI's Inter-Society Coordinating Committee for Practitioner Education in Genomics and all members of PGx team has have worked diligently to train healthcare providers and members of the general public through several outreach programs.

B. IPM REBRANDING – AWARENESS AND INFORMATION DISSEMINATION

In 2019 the IPM developed a new logo and brand alignment with UPMC and Pitt. Marketing materials, namely a brochure outlining IPM activities and focus areas, have been used in multiple settings. First, we undertook a mailing to about 5,400 regional referring physicians, including a range of specialties such as family medicine, internal medicine, cardiovascular medicine, oncology, and pediatrics. We also mailed an AAMC list and hand-curated list of precision medicine programs at other universities in the United States. All in all, we mailed out just over 6,300 brochures.

The IPM has promoted the discussion of precision medicine at Pitt and UPMC though multiple outlets including IPM Advances email blasts to all faculty of Pitt Heath Sciences since 2018, through genomeweb, through our website (ipm.pitt.edu), and via Twitter (@iPrecisionMed). These all highlight the breadth and depth of precision medicine at Pitt and UPMC.

C. IPM PRESENCE AND LEADERSHIP AT NATIONAL CONFERENCES

To raise our stature on the national stage, the IPM and its associated faculty have been actively participating in precision medicine conferences in the United States. In June 2019, Dr. Empey represented the IPM as a panel moderator at the Precision Medicine Leaders Summit and in January 2020, Dr. Empey, Mylynda B. Massart, MD, PhD, and Adrian V. Lee, PhD, participated in talks and panels at the Precision Medicine World Conference (PMWC). Further, at PMWC the IPM had a marketing booth to raise awareness of our activities and engage with other academic groups and private companies in the precision medicine field.

In September 2021, Pittsburgh will host the Precision Medicine World Conference East which will enable us to further build on the relationships developed in 2020 and allow us to form a meeting agenda to highlight key areas of strength in precision medicine in our region. The conference will have two tracks and ample opportunities for networking.

IPM booth for conferences and events.


Test 2 Learn™
Delivering personalized genomics education
test2learn.org
University of Pittsburgh
School of Pharmacy
UPMC | GENOME CENTER
NEXT GENERATION SEQUENCING AND CLINICAL MOLECULAR SERVICES
INSTITUTE FOR PRECISION MEDICINE
A partnership of the University of Pittsburgh and UPMC
Pitt
#1 PUBLIC UNIVERS
IN THE NORTHEAS
TOP 4% OF UNIVERS
GLOBALLY
TOP 5 IN NIH RESEA
SUPPORT

In 2020, IPM worked with the Center for Connected Medicine and their Annual Top of Mind conference and market survey which focused on three key areas of precision medicine, data aggregation, and patient engagement. Dr. Empey led a discussion on implementation of pharmacogenomics, and Dr. Massart was an expert panelist on the Center for Connected Medicine's "Rise of Genomics" webinar. We had planned to collaborate on a combined CCM effort on precision medicine as a lead up to the PMWC meeting, however as this meeting was delayed due to COVID this effort is also delayed.

D. PRECISION MEDICINE PILOT AWARDS AT PITT AND UPMC

In addition to the completion of our two-year 2016 pilots, in conjunction with the department of Pharmacology and Chemical Biology, we funded five new one-year pilots in 2019 with a focus on precision medicine:

- *Using Translational Therapeutics to Target the Hsp70 Chaperone in Rhabdomyosarcoma.* Jeff Brodsky, PhD, Department of Biological Sciences.
- *Precision Targeting of Non-receptor Tyrosine Kinases in Acute Myelogenous Leukemia.* Thomas Smithgall, PhD, Microbiology and Molecular Genetics.
- *Computational Repurposing of Chemotherapies for Cardiomyopathies.* Stephen Chan, MD, PhD, Vascular Medicine Institute.
- *Targeting Fatty Acid Synthesis in Platinum Resistant Ovarian Cancer.* Ben van Houten, PhD, Genome Stability Program, UPMC Hillman Cancer Center.
- *Explore Electrophilic Nitroalkenes as Rad51 Inhibitors in Triple Negative Breast Cancer.* Carola Neumann, MD, Magee-Womens Research Institute.

In 2019, the IPM further funded two categories of pilot awards in order to stimulate two of our key resources: (1) pilot projects utilizing PBC samples, and (2) pilot projects utilizing the UGC research services, as detailed above.

At the end of 2019 we launched the Precision Medicine Initiative for Commercialization (PreMIC) pilot program with PittsciVelo of the Innovation Institute, soliciting proposals for commercial translation project funding. These pilots are supported with funds from the Richard King Mellon Foundation and will provide teams $100,000 over a one-year period as well as commercial translation strategy development and commercialization support from sciVelo and the Innovation Institute.

Our RFA targeted mid- to late-stage commercial translation projects and asked that proposed project should meet one or more of the following requirements: (1) validated unmet clinical need, (2) technological proof-of-concept validation available, (3) a maturing commercial translation plan, and (4) filed invention disclosure covering the technology or be willing to work with the sciVelo team to submit a disclosure to the Innovation Institute in advance of their proposal submission. Our stated desired outcomes for funded projects at the end of a one-year funding cycle were (1) readiness for spinning out into a new company and pursuing venture capital funding, (2) transition to industry partners for further development via technology licensing, or (3) transition directly to clinical practice via technology licensing.

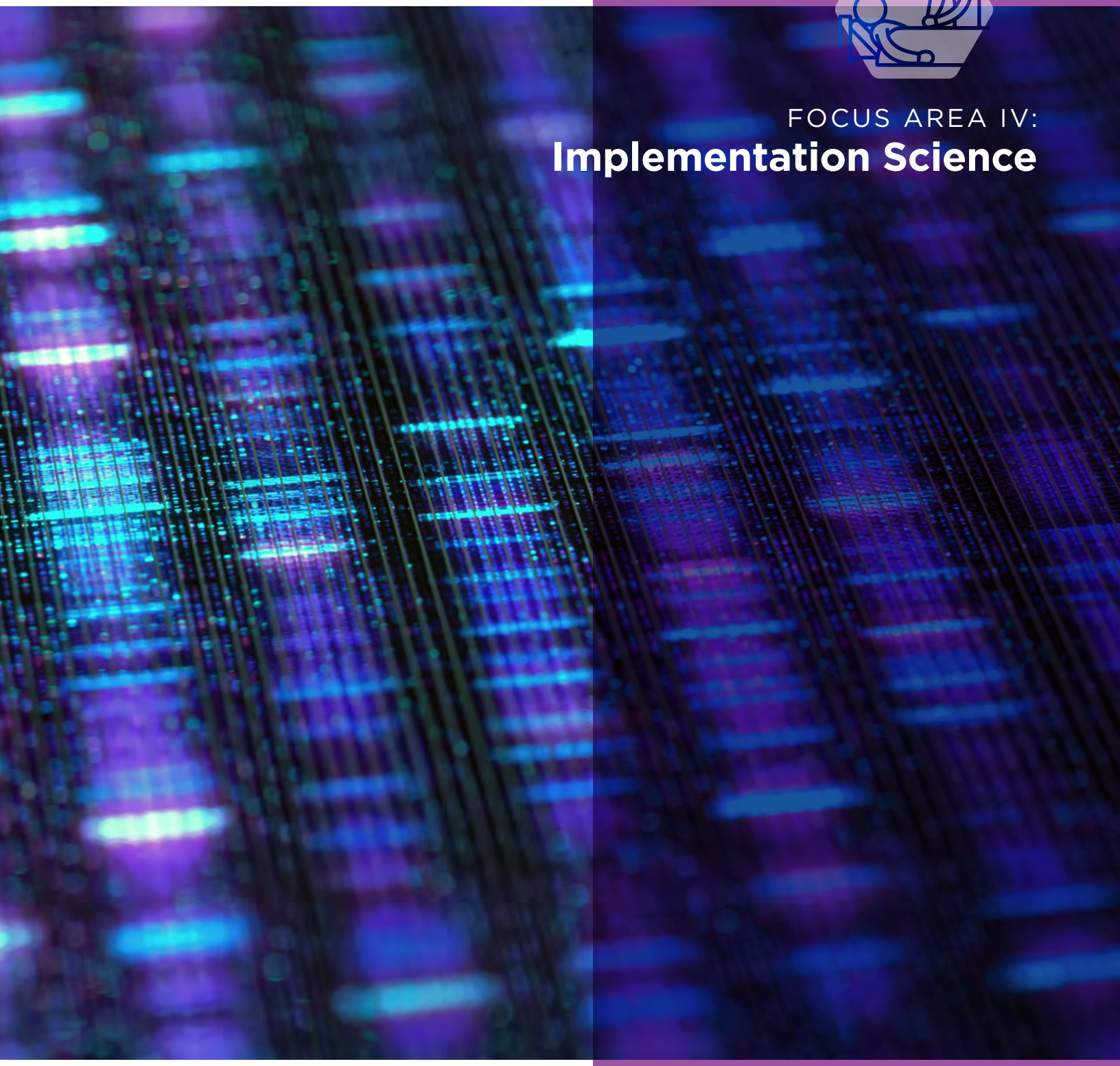
We received 15 applications for diagnostic or therapeutic commercial translation from indications including organ transplant, oncology, metabolic disorders, viral infections, inflammatory diseases, cardiovascular disease, and ophthalmology. Teams were selected to progress to a second round based on responsiveness to the funding announcement and technology readiness. After two months of coaching from sciVelo commercial translation associates, seven finalist teams pitched their precision medicine projects to the PreMIC judge panel at LifeX Ventures on February 21, 2020. The judging panel included a clinical advisory board, commercial translation assessment team, and technology readiness judging team.

Ultimately three teams were selected to receive one year of funding for their proposals based on their scores and judges' comments. Teams also receive consistent translation coaching from sciVelo and other specifically identified mentors and it is planned that Innovation Institute's commercialization team of licensing managers and executives-in-residence will advance the developed projects toward intellectual property protection, licensing, and new company creation.

The three teams selected for the 2020 funding cycle are:

- ProTeara ($100,000): Alan Wells, MD, DMSc, Shiva Swamynathan, PhD, and Ian Conner, MD, for further development of a peptide biologic to cure dry eye
- Universal CARs ($100,000): Jason Lohmueller, PhD, Alex Deiters, PhD, and Olivera Finn, PhD, for development of their Universal CAR T Cell platform technology for immunotherapy
- MALT1 PPIi ($50,000): Peter Lucas, MD, PhD, Linda McAllister, MD, PhD, Bill Chen, PhD, and Heejae Kang for next step development of precision small molecules targeting mechanisms underlying lymphoma and autoimmune diseases

These teams are now funded and working towards their milestones and second round of PreMIC will launch in early 2021.



FOCUS AREA IV:

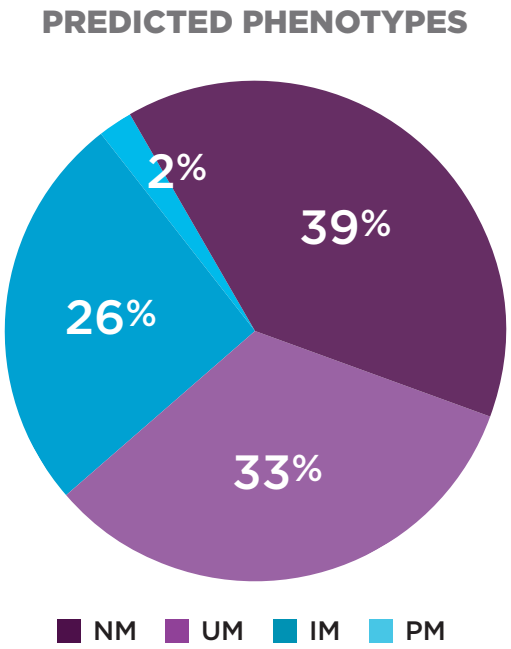
Implementation Science

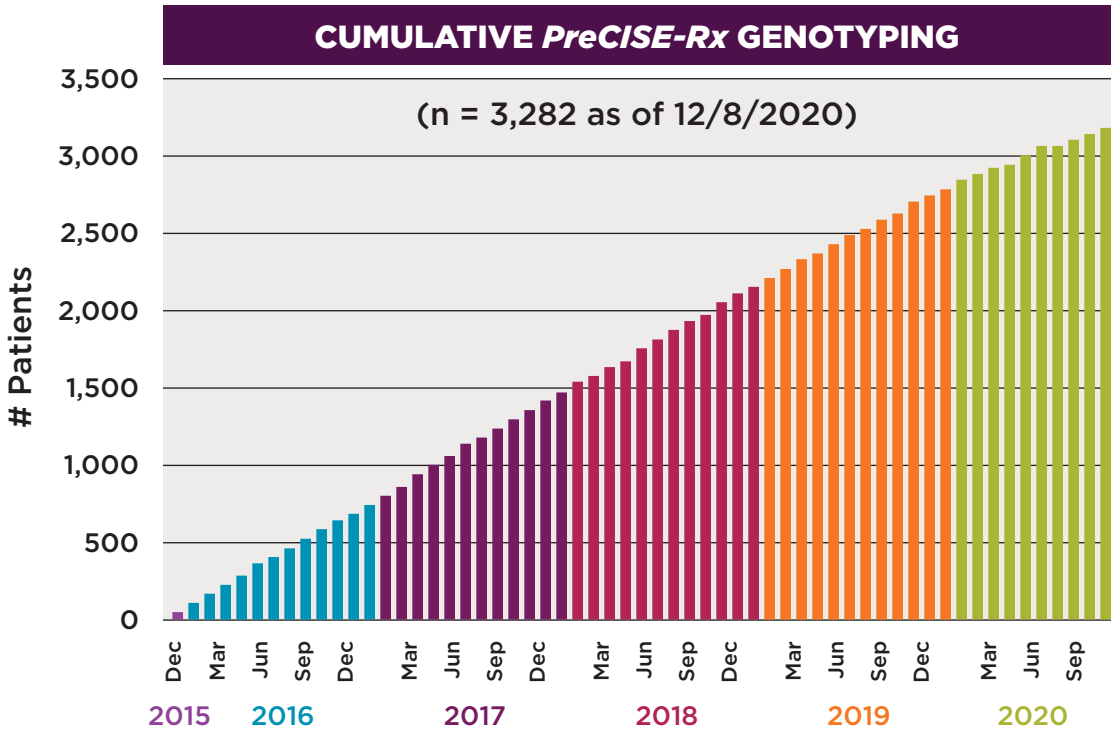
A. PHARMACOGENOMICS

Under the previous IPM leadership of Jeremy Berg, PhD, a pharmacogenomics pilot project was implemented by Dr. Philip Empey. This pilot project (PreCISE-Rx) has converted to standard-of-care genotyping in all patients and clinical outcomes are now being realized.

The PGx Center of Excellence – scaling Pitt/UPMC's leadership in precision medicine. In 2018, we established a first-of-its-kind academic-industry partnership with Thermo Fisher Scientific in the School of Pharmacy and announced the largest PGx deployment internationally to date. Through a broad coalition of stakeholders (UPMC, Pitt, CTSI, IPM, and Pharmacy) we wrote the Strategic Plan for PGx clinical implementation and research at Pitt/UPMC with the goal of population-scale preemptive, panel-based testing and return of results >150,000 patients. 2019 and 2020 was highly productive with the following major accomplishments:

- **Extending recruitment infrastructure:** Through November 2020, 6,074 UPMC patients have been recruited through CTSI Pitt+Me Discovery (institutional blood banking effort); including 750 in 2020 despite significant research restrictions due to the pandemic. We also began targeting recruitment activity such as for COVID-19 patients (partnering with Drs. Morris and McVerry) and pre-op surgery patients (with the Department of Anesthesiology and Perioperative Medicine) where there is clinical value in preemptive PGx testing. Importantly, these integrate clinical remnant sample collection and recruitment within clinical workflows to extend infrastructure.
- **High quality PGx testing:** The UPMC Genome Center has extracted DNA from 5,877 Pitt+Me Discovery samples to date with a <2% failure rate. They have undergone PGx analysis and have been bio-banked for future research. In 2020, we optimized methods, focused on biobanking software processes.





- **Completion of the PGx clinical reporting.** In summer 2020, we achieved the significant milestone of full clinical validation our new UPMC Comprehensive PGx Panel. This includes HL-7 outflows to both UPMC EHRs using discrete variable reporting. Together with the UPMC Genome Center, the PittPGx team designed this best-in-class PGx panel covering 14 genes (293 alleles) and a new, custom reporting pipeline for clinical reporting. UPMC EHR decision support upgrades (Epic) are expected in early 2021 to enable alerting for genephenotype-based clinical decision support text for 72 medications (estimated >200 alerts) that have been written by the PittPGx team.
- **Development of research pipelines.** In fall 2020, we finalized specifications for standardized genomic data outputs (e.g., VCF) with requisite linkages to patient identifiers to combine genomic data with EHR data in CTSI's Neptune data warehouse for genotype-phenotype discovery research. CTSI and DBMI also built interfaces for research cohort exploration (i2b2) to enable future research. Work to operationalize workflows for the deposit of genomic data in real time is near complete.
- **UPMC Clinical Analytics.** In 2020, we examined five years of enterprise-wide Epic prescribing data to determine the incident rate of prescribing of PGx drugs that may receive UPMC EHR alerting following return of results among 8.4 million patient encounters. This led to two NHGRI IGNITE network publications with other institutions completing similar analyses. Working with UPMC Enterprises, we're working to connect UPMC clinical genomics data with Analytics EHR data to produce dashboards capable of tracking the clinical value of these data.

Overall, UPMC provider and patient enthusiasm for PGx results remains extremely high with 96% of Pitt+Me Discovery participants choosing to receive their personal results and to deposit these actionable test results in UPMC EHRs for their providers. In 2020, our dissemination efforts have led to multiple abstracts and platform presentations (e.g., at ASHG, PMWC, PGRN, AACP, ACCP, PLUGS); >10 publications, and numerous media mentions. We also had several external industry groups approach us to leverage our services for contract work (i.e., PGx testing at the UPMC Genome Center or Magee Cytogenetics lab).

PreCISE-Rx, the UPMC clinical implementation program: Through novel clinical services we successfully deployed a scalable model for genomics implementation at UPMC. As of December 1, 2020, 3,282 patients have undergone standard of care CYP2C19 testing at UPMC Presbyterian; 922 (28.1%) carried loss-of-function variants and 621 (18.9%) had actionable results (change in therapy). An additional 770 (23.4%) were evaluated for potential step-down therapy (cost saving). Through the UPMC Pharmacogenomics Service, pharmacists have written consults on all genotyped patients, educated providers, and worked closely with EHR teams to build alerts in both Epic and Cerner.

We previously reported that testing improved patient outcomes. Specifically, that the risk for major adverse cardiovascular events after cardiac stenting was significantly higher in patients with a loss-of-function allele prescribed clopidogrel versus alternative therapy (PMID: 29102571) and our implementation strategies of 12 early adopter institutions for CYP2C19 (PMID: 29280137) and CYP2D6 (PMID 30894703). In 2020, our economic analysis showed that genotype-guided escalation of antiplatelet prescribing had the highest probability of being cost-effective across conventional willingness-to-pay thresholds ($42,365/QALY) (PMID 32042096). We also published the impact of the CYP2C19*17 allele on cardiac on outcomes (PMID: 32897581) and on the reusability of CYP2C19 genotyping results (PMID: 32678355). In the latter, we reported that 42% of patients had a subsequent drug-genotype interaction prescribing event that occurred at an average of 25 days after the initial genotyping. With IPM funding from the Lowenstein Foundation, we also developed machine learning approaches incorporating PGx data and reported our methods could better predict bleeding after cardiac stenting over standard clinical algorithms; work that was selected as a high-profile platform presentation at the ACCP Annual Meeting in fall 2020.

B. IMPLEMENTATION OF WHOLE GENOME SEQUENCING IN THE NICU

Studies show that 2-3% of children are born with genetic abnormalities and one in 200 babies have an inborn error in metabolism. Genetic abnormalities result in 40% of childhood mortality and 50% of hospital admissions. Recent international publications have supported the cost-effectiveness of rapid whole exome sequencing (WES) and whole genome sequencing (WGS) for rapid diagnoses and decreased NICU stays, as well as positive long-term health and economic outcomes. Utilizing the new UPMC Genome Center, the neonatal intensive care units (NICU) at UPMC Children's Hospital of Pittsburgh and UPMC Magee-Womens Hospital are poised to determine the diagnostic value and health benefits of rapid WGS. We were able to attract Richard King Mellon Foundation funding for implementation of WGS in our healthcare system.

We successfully assembled the team of required experts for the design and implementation of the NICU sequencing project (Project PISCES) which received IRB approval in 2020 and enrolled its first patients. Patients are identified and enrolled upon entry to the NICU and they receive WGS in parallel to standard clinical care. Clinicians typically evaluate six to 10 patients per day for possible enrollment. Following informed consent and sample collection, WGS is conducted at the UPMC Genome Center with interpretation in conjunction with the Clinical Genetics Laboratory at Magee. In a similar study in which sequencing is not performed in-house (Project GEMINI) our physicians have used WGS to rapidly diagnose genetic disorders which have led to early interventions key to patient survival or led to redirection of care. Examples include abnormalities in the following genes:

1. NPHS1 gene, consistent with a diagnosis of nephrotic syndrome, type 1, a severe form of kidney disease
2. ACAD9 gene, consistent with a diagnosis of mitochondrial complex I deficiency which is incompatible with life
3. NR3C2 gene, consistent with a diagnosis of pseudo-hypoaldosteronism type 1, a disorder associated with salt wasting in the neonatal period, with life-threatening elevated potassium levels and metabolic acidosis
4. Aacid alpha-glucosidase, consistent with a diagnosis of Pompe disease, an often fatal disorder that disables the heart and skeletal muscles

Now that our own in-house study in underway (PISCES), we are excited to enroll patients and demonstrate the value of this approach to families in the Pittsburgh region specifically, as well as adding to the growing body of evidence nationally. As of January 2021, 12 infants have been enrolled and WGS completed on the majority.

C. THE PRIMARY CARE PRECISION MEDICINE CLINIC (PCPM)

The PCPM clinic launched officially in July of 2019 to meet the needs of patients seeking care with the applied definition of precision medicine integrating genetics, family history, and environmental exposures, and the clinic has continued to grow through 2020. The clinic is led by Pitt faculty member Mylynda B. Massart, MD, PhD, and its multidisciplinary team now consists of two genetic counselors, a clinical pharmacist, and a licensed clinical social worker. Since November 2019 the PCPM clinic has conducted over 500 patient visits with 172 new referrals and currently runs one day per week. New referrals from both major health systems in our region included interpretation and clinical validation of direct-to-consumer test results, genetic cancer risk assessment, pharmacogenomics, and specialty genetic testing such as neurogenetic testing.

The majority of visits converted to telehealth in March of 2020 due to COVID-19 and this has been a successful transition to improve access to services and remove geographic constraints of referrals. We recently were consulted by West Virginia University Health System to deliver this service to their patients which is not available in their region. The patients seen over the last year have resulted in the recommendation or facilitation of 63 tests from numerous genetic testing companies and whole genome sequencing on two research families at the UPMC Genome Center. In addition to clinical patient care, the team has completed a scope analysis of genomic services provided across the UPMC health system, launched efforts to establish institutional billing for genomic testing on the adult side, and internal ordering and billing for clinical whole exome and whole genome sequencing from the UPMC Genome Center. The team has provided several lectureships locally and nationally over the last year to present the structure and vision of the PCPM clinic and two papers are currently in draft for publication to disseminate clinic structure and early lessons learned from this novel clinical implementation of clinical genomics.

Example patients from the first year and a half:

1. Patient was referred by a neurosurgeon for genetic testing of worsening weakness and spasticity in the legs and neuropathy that was not consistent with clinical findings. The patient had progressive intermittent symptoms for more than 10 years with sudden worsening over the last two years. A targeted next-generation sequencing panel for ataxia was obtained showing a novel likely pathogenic variant in the KIF1A gene which is responsible for transporting vesicles of neurotransmitters along neurons in the brain. The variant causes a premature stop codon for gene expression. Although many other disease-causing mutations have been seen in this gene, this particular mutation had not been previously reported and could only be categorized as likely pathogenic. The PCPM team identified and partnered with a research team in Japan that studies this gene/protein function in a worm model and the research team generated this patient's mutations and performed functional studies which confirmed the protein was nonfunctional and could not transport vesicles. This provides further evidence that this patient's mutation is pathogenic and functions in an autosomal dominant manner.

2. Patient underwent direct-to-consumer (DTC) genetic testing to see if she could find her birth family since she was adopted. She found her family and also found out that she was Ashkenazi Jewish and that several family members had died of cancer. The patient presented for possible BRCA testing. Due to lack of known mutation in family, a broader cancer panel was recommended, and ATM mutation was identified. The patient is now referred for high-risk screening and management.

3. Patient presented with their father, MS, for primary care in the context of known BRCA2 mutation. The patient had previously taken results to a PCP who did not know what to do with them. In addition, there were two other sisters of CS, daughters of MS, who were adults and had not been tested. Both known carriers were referred for high-risk screening and management and the two sisters were subsequently tested for familial mutation.

4. Patient was gifted DTC testing for the holiday. Results returned with a prothrombin mutation and the patient remembered that two cousins had clots/PE. Confirmatory clinical testing was done, and prothrombin mutation confirmed. Preventive treatment guidelines were reviewed and instituted with the patient to decrease her personal risk of clot formation.

5. Patient with atypical multiple sclerosis (MS) who has been a quadriplegic since age 30 was referred for hereditary neuropathy panel testing. VUS was identified in GARS gene which has other mutations associated with a similar type of symptoms. Currently working with numerous affected and unaffected patients to determine whether the VUS is pathogenic or not. If VUS is not travelling with the MS- like phenotype then plans are to proceed with WGS and comparative analysis with family members at the UPMC Genome Center.

D. BIOETHICS AND HEALTH CARE POLICY

Investigators within IPM interact with the Center for Bioethics and Health Law. For example, implementation of large-scale genomic sequencing such as in pharmacogenomics and assessment of disease risk and outcome will require careful thought and implementation of bioethics and policy. Lisa Parker, PhD, professor and director of the Pitt Center for Bioethics & Health Law, has been involved in many ongoing discussions including the access to human specimens from those outside the university and the NICU sequencing project.

SUMMARY

The last year and a half saw a significant awareness in precision medicine both nationally and in Pittsburgh. Pitt and UPMC remain well placed to become national leaders in this area. The IPM has forged collaborations in many areas of precision medicine research at Pitt/UPMC both with the development of core resources and infrastructure and research implemented into clinical care. While IPM is a virtual institute, the long-term goal is to have a defined location that will house many of the components key to precision medicine research such as genomics, biobanking, and research.

INSTITUTE FOR PRECISION MEDICINE LEADERSHIP

Adrian V. Lee, PhD, Director

Annerose Berndt, PhD, DVM, Associate Director, Genomics Services

Philip Empey, PharmD, PhD, Associate Director, Pharmacogenomics

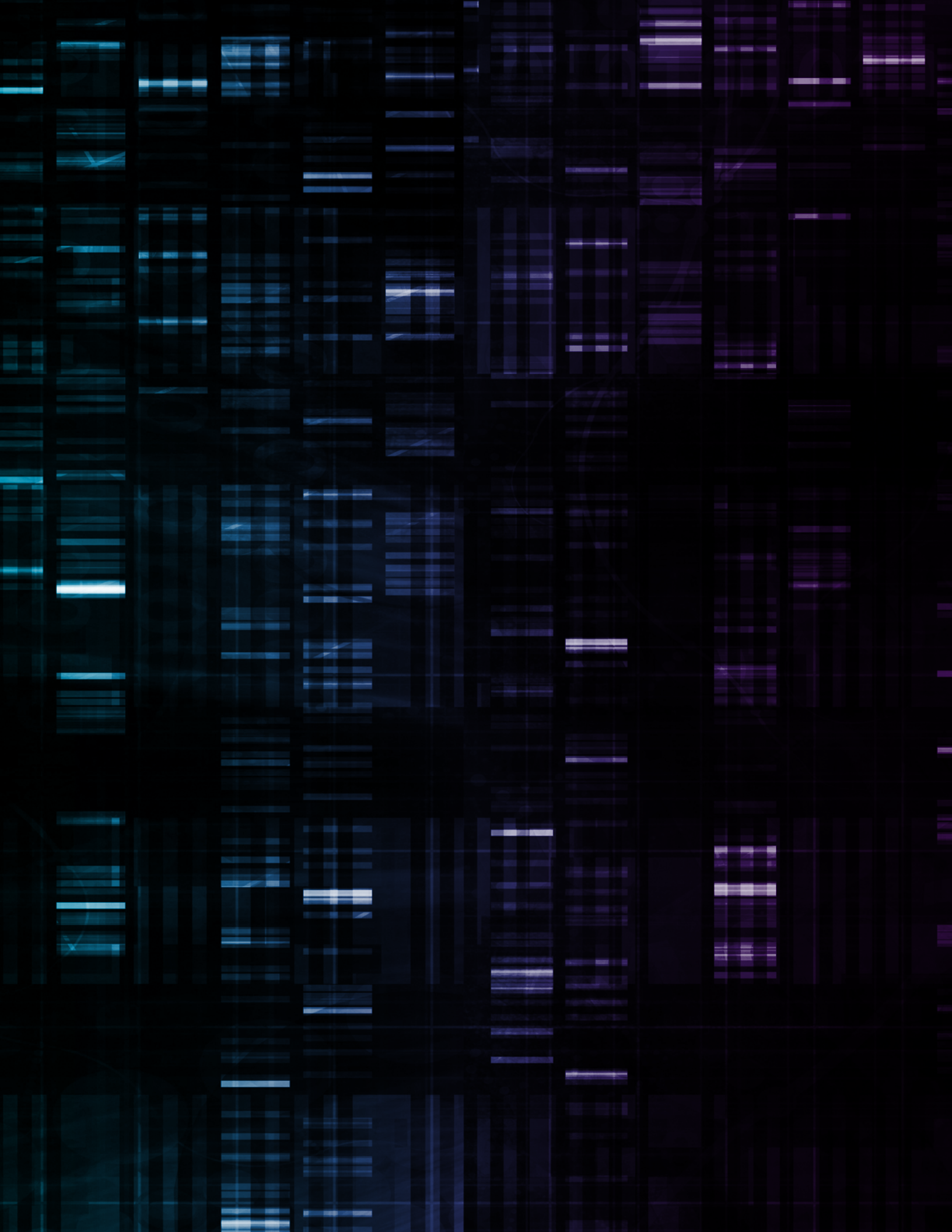
Peter Lucas, MD, PhD, Associate Director, Pathology

Mylynda B. Massart, MD, PhD, Associate Director, Clinical Services

Lisa S. Parker, PhD, Associate Director, Bioethics

Jonathan C. Silverstein, MD, MS, FACS, FACMI, Associate Director, Research Informatics

Jennifer M. Xavier, Associate Director, Research



UPMC
LIFE CHANGING MEDICINE

University of Pittsburgh

Institute for Precision Medicine
204 Craft Ave., Room A412 | Pittsburgh, PA 15213 USA
Phone: 412-641-7557 | Fax: 412-641-2458

SYS519695 TS/AK 0521