PRECISION MEDICINE

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Dear Colleagues,

Over the past year, The Columbia Precision Medicine Initiative (CPMI) has continued to grow with more critical recruitments, conferences, and pilot awards, and with the engagement and collaboration of faculty and leadership throughout the University. Under Dr. Muredach Reilly's leadership, the NIH funding for the Clinical and Translational Science Award Program was renewed, with an award of $61.7 Million to accelerate development of new treatments and improve patient care. Congratulations to Muredach and his team!

We are delighted to welcome Dr. Gamze Gursoy to the Dept. of Biomedical Informatics, Vagelos College of P&S., who is an expert on privacy and the genome. Gamze has a secondary appointment in computer science, and is a jointly appointed to the New York Genome Center. We also look forward to welcoming Dr. Tarjinder (T.J.) Singh to the Dept. of Psychiatry, who is an expert on the genetic architecture underlying psychiatric disorders. T.J. is jointly appointed the the Zuckerman Institute and the New York Genome Center. Both appointments were made possible by financial support from the Diana and Roy Vagelos Precision Medicine Fund.

Please read more about their research later in this newsletter.

Last year, we formed a Precision Medicine Coordinating Committee. Members come from across the entire university to share their precision medicine research and find ways to collaborate. One of the outcomes of these meetings was the recognition that the field of Exposomics is an important and growing area of precision medicine. In December 2021, we held a symposium on the Exposome. We are grateful to Drs. Gary Miller and Andrea Baccarelli of the School of Public Health for their efforts in organizing this meeting. In the coming months, the initiative will look to promote university-wide collaborations in this field.

One of the goals of CPMI is to promote Precision Medicine education at all levels. We asked Drs. Rachel Adams (English), Gil Eyal (Sociology) and Sam Sternberg (Biochemistry) to create and teach a new undergraduate course for Fall 2022. They are currently developing the syllabus, and we thank them for their efforts. In addition to covering the science that is the basis of precision medicine, the course will include fundamental humanistic questions and challenges raised by this discipline.

We are currently reviewing applications for the Roy and Diana Vagelos Precision Medicine Pilot Awards. This program, now in its fifth year, has stimulated collaboration across all three Columbia campuses, has led to external funding, and high visibility publications.

The Precision Medicine and Society program, chaired by Drs. Paul Appelbaum, MD and Gil Eyal, PhD, sets Columbia apart from other precision medicine initiatives by focusing on ethical and equity issues in the impact of precision medicine.

Our fifth academic conference, Advances in Precision Medicine: Genetics of neurodevelopmental disorders, provided a full day of high impact international speakers covering basic and applied science in this field of precision medicine. We look forward to hosting our sixth conference on April 5th, 2022, which will focus on technology innovation and functional genomics in precision medicine.

I would like to take this opportunity to thank Dr. Roy Vagelos for his continuing scientific and medical leadership in precision medicine, and his generous gift to the Precision Medicine Initiative. The gift is being used to fund a number of critical recruitments in precision medicine research, and the infrastructure required to advance basic science.

A more detailed description of progress in the Precision Medicine Initiative during the past year and further details of the activities during the coming year is provided in this newsletter.

Tom

Tom Maniatis, Ph.D.
Director of Columbia University Precision Medicine Initiative; and the
Isidore S. Edelman Professor in the Department of Biochemistry & Molecular Biophysics

Advances in Precision Medicine Conference: Genetics of Neurodevelopmental Disease

Fifth Annual Columbia Precision Medicine Initiative (CPMI) conference, Advances in Precision Medicine: Genetics of Neurodevelopmental Disease.

The recent past has seen major advances in the understanding of the genetic and genomic architecture of neurodevelopmental disorders. We now have a deeper understanding of how genetic risk for many complex traits including neurodevelopmental disorders is driven by natural selection and distributed across the allelic spectrum.

While reliable results have emerged for conditions ranging from schizophrenia to bipolar disorder to autism, providing important insights into aspects of the neurobiology of these syndromes, a comprehensive understanding of their underlying biology is still out of reach.

In addition to the emerging genetic and molecular advances, there is the increasing realization that neurodevelopmental disorders target specific brain circuits. The interaction between genetic background, brain structure, and brain function is now the scientific background upon which specific neurodevelopmental conditions can be studied and understood.

Please click the links below for the available recording, or visit our [video library here](#).

Moderated by Thomas Lehner, PhD, MPH
[Mark Daly, PhD, Harvard Medical School, University of Helsinki](#)
Elise Robinson, ScD, Harvard T.H. Chan School of Public Health
[Matthew State, MD, PhD, University of California, San Francisco](#)
[David Goldstein, PhD, Columbia University](#)
[Sergiu Pasca, MD, Stanford University](#)
Nenad Sestan, MD, PhD, Yale School of Medicine
[Kristen Brennand, PhD, Yale School of Medicine](#)
[Huda Zoghbi, MD, Baylor College of Medicine](#)

The 5th Annual Columbia Precision Medicine Initiative (CPMI) conference: Advances in Precision Medicine: Harmonizing Clinical and Genomic Data was held on April 7, 2021 via Zoom. [The event program can be found here.](#)

SAVE THE DATE

6th Annual Advances in Precision Medicine

Conference Genomic Innovation and Precision Medicine:

Reading, Imaging, Editing, and Writing the Genome

The Forum, Manhattanville Campus

[Register Today!](#)

April 5, 2022

Precision Medicine Scholar's Day

On November 5, 2021, the Vagelos College of Physicians and Surgeons Columbia Precision Medicine Initiative, Irving Institute for Clinical and Translational Research and the Herbert Irving Cancer Research Center presented Precision Medicine Scholars' Day featuring research presentations by the Pilot Award winners.

Event Program can be downloaded [here.](#)

Symposium on the Exposome

On December 17, 2021, the Precision Medicine Initiative hosted a hybrid symposium focused on environmental factors in human disease. The Director of the National Institute of Environmental Health Sciences, Rick Woychik, gave the keynote speaker with several Columbia- based investigators addressing how to incorporate environmental exposures into studies. In addition to geospatial approaches, this meeting explored the utility of using the exposome framework (high-resolution mass spectrometry, environmental epigenetics) to provide comprehensive analysis of complex exposure in human samples.

Selected talks included:

Keynote Address: The environment at NIH: Richard Woychik, PhD, Director of the National Institute of Environmental Health Sciences, National Institutes of Health

Exposomics at Columbia:Gary W. Miller, PhD-Department of Environmental Health Sciences, Mailman School of Public Health

Characterizing consequences: epigenetics and extracellular vesicles in environmental health
Andrea Baccarelli, MD, PhD-Department of Environmental Health Sciences, Mailman School of Public Health

More details can be found on our website **[here.](#)**

Faculty Announcements

Gamze Gürsoy, PhD

Gamze Gürsoy is an incoming Assistant Professor at the Department of Biomedical Informatics at Columbia University and a Core Member at the New York Genome Center, starting January, 2022. She will also be affiliated with the Department of Computer Science. Her research group will develop tools to analyze and understand large-scale omics data in relation to diseases and phenotypes with a particular interest in developing privacy-preserving software, file formats, and pipelines that enable broad sharing and analysis of sensitive genotypic and phenotypic data in public servers. Dr. Gürsoy is also interested in developing tools to map the regulatory wiring of the chromatin to interrogate the regulatory variation affecting the molecular phenotypes associated with diseases. Much of her lab's work focuses on creating reproducible, efficient, easy-to-use, and cloud-ready tools for the broad biomedical community. The computational work in the lab will be supported by experimental approaches, creating opportunities for trainees in cross-disciplinary studies. More information can be found here.

Tarjinder (TJ) Singh, PhD

Tarjinder Singh is a postdoctoral fellow in Dr. Mark Daly's group. He completed his PhD in 2016 at the Wellcome Trust Sanger Institute, where he studied the role of rare variation in the genetic architecture of psychiatric and neurodevelopmental disorders. Mentored by Dr. Daly and in close collaboration with Dr. Benjamin Neale's group, he currently works on the meta-analyses of sequencing data in psychiatric traits, with a primary focus on the genetics of schizophrenia.

Updates

Institute for Genomic Medicine

As of November 1, 2021, Dr. Ali Gharavi is the Interim Director of the Institute for Genomic Medicine, succeeding Dr. David Goldstein. Dr. Gharavi is the Jay Meltzer Professor of Nephrology and Hypertension at Columbia University Vagelos College of Physicians and Surgeons. He serves as the chief of the Division of Nephrology at NewYork-Presbyterian/Columbia University Irving Medical Center and is the director of the Center for Precision Medicine and Genomics (CPMG) in the Department of Medicine. Dr. Gharavi, already immersed in the scientific and educational missions of the IGM, joined Columbia University in 2003. He is an internationally renowned expert in the genomics and genetics of kidney diseases and his research has led to the discovery of genes and loci for IgA nephropathy and congenital defects of the kidney and urinary tract. In collaboration with Dr. Goldstein and IGM investigators, Dr. Gharavi recently demonstrated the utility of sequencing for the diagnosis and management of patients with kidney failure. As the Interim Director of the IGM and a principal investigator of the NIH All of Us program, he will aim to expand genomic medicine programs at VP&S and CUIMC across diverse disciplines and populations.

Over the past year, the Institute for Genomic Medicine (IGM) has continued to make precision medicine a reality across the medical center. In partnership with several clinical departments, the IGM is breaking new ground in the clinical application of genomics across lifespans of individuals and toward investigations of disease-causing mutations in the laboratory to provide personalized medicine in the clinic.

In the first analysis of its kind, researchers at Columbia University Vagelos College of Physicians and Surgeons and several other institutions have linked distinct patterns of genetic mutations with obsessive-compulsive disorder (OCD) in humans. In collaboration with Johns Hopkins University, Dr. Goldstein's team took a genome wide approach, which uses high-throughput sequencing and computational biology techniques to identify relevant genes anywhere in the genome. The work, published online June 28 in Nature Neuroscience, confirms the validity of targeting specific genes to develop new OCD treatments and points toward novel avenues for studying this often-debilitating condition.

In another study led by Dr. Goldstein and IGM Member Ronald Wapner, MD, new genes were identified that have been implicated in stillbirth, significantly increasing the understanding of the condition's genetic foundations. Using both standard and advanced analysis techniques, the team identified the likely genetic cause of stillbirth in about one of every 10 cases studied. The study was published in the New England Journal of Medicine; an editorial was also published about the significance of the study. The study was conducted with the Department of Obstetrics & Gynecology at Columbia University Vagelos College of Physicians and Surgeons.

Results of one major clinical and research collaboration were published in March of this year in *Nature Metabolism*. The study identified rare, causal genetic variants in a gene responsible for a progressive, late-onset retinal degenerative disease known as Macular Telangiectasia Type 2.   Using the recently developed method "collapsing analysis", this study identifies the typical disease phenotype, and suggests potential therapeutic options to prevent vision loss in many affected patients. The study was conducted by the Department of Ophthalmology with the Department Pathology & Cell Biology and IGM at Columbia University Vagelos College of Physicians and Surgeons.

Through a project led by the IGM, the bioinformatics team presented ATAV – an analysis platform for large-scale whole-exome and whole-genome sequencing projects. Their work was published in *BMC Bioinformatics*. The ATAV platform provides access to the largest variant databases, and it can be easily deployed by other groups that are building their own platforms, databases and/or user interfaces. This platform is different from existing platforms in its ability to show data of newly-added samples and sequences in real-time.

In an upcoming publication in Genetics in Medicine, IGM investigators report their approach to advancing genetically stratified medicine by implementing broad exome sequencing (ES) infrastructure and research protocols at Columbia University Irving Medical Center/NewYork-Presbyterian Hospital (CUIMC/NYPH). Altogether 4889 adult and pediatric probands from CUIMC/NYPH were enrolled, leading to primary genetic diagnoses in 572 probands across multiple disease areas (e.g. epilepsy, chronic kidney disease, fetal anomaly). New gene-disease associations and phenotypic expansions were discovered across these clinical specialties.   The participants are being re-contacted with updated genetic diagnoses or for participation in future genotype-based clinical trials.

Irving Institute for Clinical and Translational Research

In the past year the Precision Medicine Resource team of the Irving Institute continued establishing new and supporting existing programs focused on providing funding opportunities, research services, and workforce development for implementation of this emerging domain of medicine in clinical practice.

As part of the highly successful collaboration between the Columbia Precision Medicine Initiative, Irving Institute, and Herbert Irving Comprehensive Cancer Center teams led by Melanie Brazil, PhD, Alexander Fedotov, PhD, Emer Smyth, PhD, and Tanisha Jackson, PhD, five new interdisciplinary cohorts of investigators were selected to receive one-year Precision Medicine Pilot awards to support research projects focused on a wide range of topics from basic, pre-clinical and clinical precision medicine domains (2021 award-winning teams are listed below). These projects continue to be supported in part by funding from the Pilot Translational and Clinical Studies initiative of the Clinical and Translational Science Award (CTSA) to the Irving Institute from the National Center for Advancing Translational Sciences (NCATS) of the NIH.

On November 5, 2021, research accomplishments of past and current pilot award recipients were celebrated at the annual symposium "Precision Medicine Scholars Day", hosted in the virtual format jointly by the CPMI, Irving Institute, and HICCC teams.

The one-semester Vagelos College of Physicians and Surgeons graduate course "Introduction to Precision Medicine", directed by Wendy K. Chung, MD, PhD, Ronald Wapner, MD, and Krzysztof Kiryluk, MD, was offered by the Resource for the fifth consecutive year and allowed a new cohort of medical and other health sciences scholars to gain insights into diverse precision medicine topics, such as genomic medicine, digital health, exposomics, and others.

Now in its seventh year, a monthly seminar series "Advances in Precision Medicine" continued to offer Columbia community an opportunity to learn about most recent advances in the field directly from top precision medicine leaders from around the globe. To enable direct communication, sharing, and collaboration among current (and future) NIH NCATS CTSA Program hubs with a Precision Medicine focus, the Resource continued supporting a Precision Medicine Discussion Forum.

In addition, this year the Resource played a key role in several other university precision medicine initiatives, including establishment and management of Columbia University Biobank, publication of new "Cases in Precision Medicine" of the review series being published in the Annals of Internal Medicine journal, establishment and management of the Precision Medicine team within the EpicTogether tri-institutional consortium, and support of the fourth phase of the NHGRI-funded eMERGE project, among many others.

BRIDGE Biobank

The Columbia University Biobank (CUB) was established in 2020 as CUIMC's first institutionalized central resource of biospecimens linked to health data. CUB activities were accelerated during the pandemic to enable COVID-related research across the CUIMC campus and beyond. In partnership with Dr. Kevin Roth and the Department of Pathology and Cell Biology, CUB was able to collect over 110,000 biospecimens (including DNA, RNA, NP swabs, serum, plasma, urine, and other tissue samples) from approximately 16,000 patients tested for SARS-Cov-2 at CUIMC/NewYork-Presbyterian Hospital (CUIMC/NYP). Given the number of patients treated for COVID-19 at CUIMC/NYP and the diversity of our patient population, Columbia's COVID-19 biobank is arguably the largest and most distinct in the United States. With support from Dr. Muredach Reilly and the Irving Institute for Clinical and Translational Research, the CUB has consented more than 3,500 patients for collection of biological samples, access to electronic health records, re-contact for participation in additional research studies, replenishment of depleted samples, genomic research, and return of results.

As of December 2021, over 220 requests to the biobank were reviewed by the CUB Sample and Data Access Committee, led by Dr. Daichi Shimbo. To date, more than 22,000 samples have been disbursed to support a wide range of research studies across the CUIMC community, including the Mailman School of Public Health Departments of Environmental Health Sciences and Epidemiology, Departments of Biomedical Engineering, Systems Biology, Surgery, Pediatrics, OBGYN, and Neurology, and Divisions of Infectious Diseases, Digestive and Liver Diseases, Immunology, Pulmonology, and Cardiology within the Department of Medicine. Data from whole exome sequencing, as well as host and virome RNA sequencing, has been generated on more than 1,000 patients diagnosed with SARS-Cov-2 and is currently available in AWS for download with the appropriate IRB and CUB approvals. Whole genome sequencing is currently underway in the Institute for Genomic Medicine (IGM), and data will be available in the coming months. We encourage you to apply to use these research resources through the CUB website.

While CUB was initially focused on COVID-19 due to obvious needs, we are beginning to look past the pandemic towards University-wide recruitment efforts, with the ultimate goal of enrolling all CUIMC/NYP patients. To this end, we are partnering with clinical groups across campus on consent and sample collection, including IGM's All of Us team, Department of Emergency Medicine, Department of Pediatrics, Department of Surgery, Irving Institute for Clinical and Translational Research, and the Herbert Irving Comprehensive Cancer Center.

In recognition of the need to engage with the Upper Manhattan community that supports it, the CUB has engaged in strategic planning for long-term, collaborative community engagement.   A core workgroup was instituted in August 2021, led by Olajide A. Williams, MD, MS, and Rafael Lantigua, MD. The group recently finalized a multifaceted strategy designed to engage CUIMC researchers, biobank subjects, as well as the Upper Manhattan community in order to educate stakeholders on biobanking aims and processes, disseminate findings from research supported by the CUB, as well as keep biobank participants engaged long-term through retention activities.

Precision Medicine Publications

Led by Krzysztof Kiryluk, MD, the Resource team joined forces with a diverse group of Precision Medicine experts across the CUIMC to publish 12 articles in the Annals of Internal Medicine on various topics in Precision Medicine including a series of 10 case studies, each dealing with a common clinical issue regarding precision medicine.

A current list of publication from the series:
Precision Medicine in Internal Medicine: Overview of the series
Precision Medicine for Clinicians: The Future Begins Now: Editorial

The Role of Pharmacogenetics in Precision Prescribing.
When Patients Present With Direct-to-Consumer Genetic Test Results.
Should You Participate in a Study Involving Genomic Sequencing of Your Patients?
Genetic Assessment After a Sudden Cardiac Death in the Family.
The Role of Tumor and Germline Genetic Testing in Breast Cancer Management.
APOL1 and Genetic Testing in the Evaluation of Chronic Kidney Disease and Potential Transplant.
Concerns About Privacy and Discrimination After Genomic Sequencing.
A Personalized Approach to Stroke and Cardiovascular Risk Assessment in Women.
The Role of Polygenic Risk Scores in Breast Cancer Risk Assessment.
Genetic Testing to Predict Future Risk for Disease in a Healthy Patient

Targeted Research and Exploration Advancing Trial Models, Editing, and Next-generation Therapies (TREATMENT)

The Targeted Research and Exploration Advancing Trial Models, Editing, and Next-generation Therapies (TREATMENT) program was established by Dr. Wendy Chung to expand our capacity to care for patients with rare genetic diseases, understand the natural history and molecular mechanisms of genetic diseases, and develop new treatments for these conditions. The program was established to make Columbia a destination medical center for a growing international network of patients and families and serve as a nucleus of physicians and scientists in academia and industry working together toward cures for rare genetic diseases.

Wendy Chung. Photo: John Abbott.

We are developing novel molecular methods of treatment including the use of antisense oligonucleotides, gene addition, and gene therapy. We have expanded our Research Collaboration with Ovid for the development of treatments for patients with neurogenetic disorders, including KIF1A associated neurological disorder and HNRNPH2. We are currently participating in clinical trials of new treatments for genetic disorders including rare genetic forms of obesity, epidermolysis bullosa, and glycogen storage disease and have patients from around the United States participating in these trials. We hold regular family meetings to disseminate of experience with rare diseases to patients, families, and their providers around the world. TREATMENT unites families, patients and families and provides them with hope for a brighter future.

EpicTogether
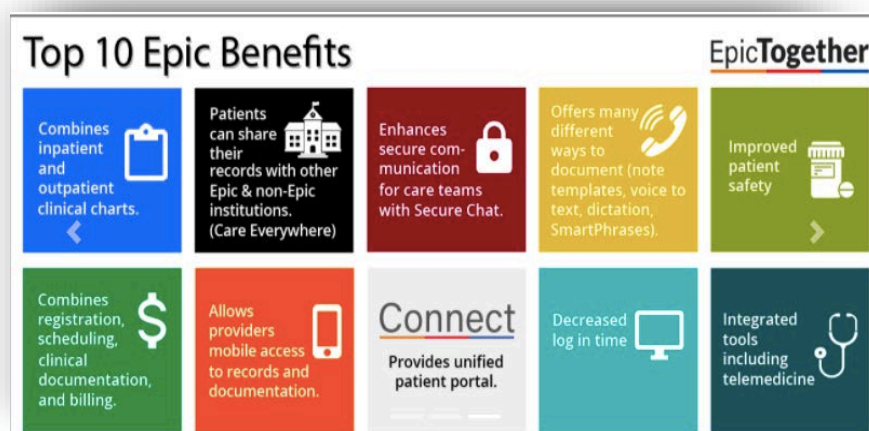
EpicTogether, the operational managing team for New York Consortium Epic implementation, has established a Precision Medicine team with dedicated analysts to work on Epic's new Genomic module and other activities around genomic data. A collaborative group representing the 3 institutions (NYP, Columbia, Cornell) is developing the infrastructure to identify genomic lab tests, convert test results to genomic clinical indicators, and develop appropriate Best Practice Advisory alerts. The initial focus was on Clinical Pharmacogenetics Implementation Consortium (CPIC) recommended guidelines for actionable pharmacogenetic results, with a recent expansion to include three CDC Tier 1 genomic applications with evidence-based guidelines. Additionally, a genomic variant entry tool was implemented to enable documentation of discrete variant data, in essence creating a hospital-wide repository of genomic variants. This feature in combination with Epic's reporting capabilities will allow providers to create custom, on-demand queries of the hospital-wide variant data. A family history tool is being built. The team will continue to champion, set goals and develop procedures for Precision Medicine data capture and alerting in Epic EHR.

Electronic Medical Records and Genomics (eMERGE) network

On July 1, 2020, the National Institutes of Health announced that Columbia University was selected to be one of ten sites from around the United States to form a Genomic Risk Assessment and Management Network as part of the fourth phase of the Electronic Medical Records and Genomics (eMERGE) project. Having been part of this initiative since 2011, Columbia eMERGE team co-led in this phase by investigators Chunhua Weng, PhD, Wendy Chung, MD, PhD, George Hripcsak, MD, Krzysztof Kiryluk, MD and managed by Alexander Fedotov, PhD will establish protocols and methodologies for improved genomic risk assessments in diverse groups and their integration in clinical care. Representing one of six enhanced diversity sites in the network, the team has developed methodologies for recruitment of participants from racial and ethnic minority populations, underserved populations, and populations who experience poorer medical outcomes, to conduct and validate genomic risk assessment for 10 common complex diseases of public health importance. Efforts on investigating ELSI issues related to the return of health risk predictions to diverse patients through focus groups are also underway.
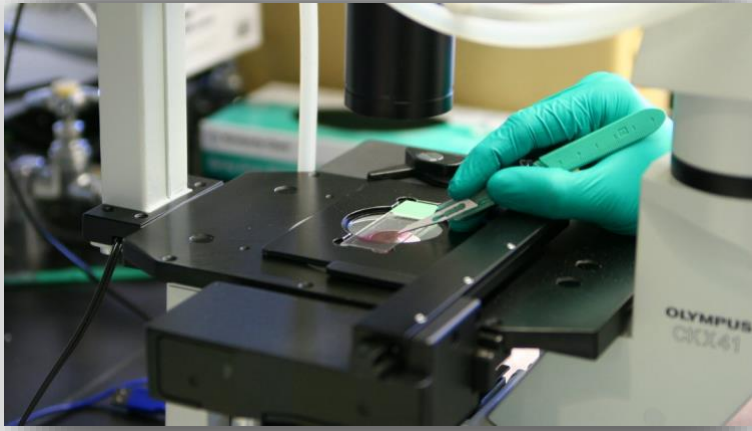
Precision Genomics Laboratory (PGL)

The mission of the Precision Genomics Laboratory, a joint initiative of the Department of Pathology and Cell Biology and the Institute for Genomic Medicine, is to apply advanced genomic science in a clinically actionable setting to improve the diagnosis and treatment of human disease.

This CLIA/CLEP certified and CAP accredited laboratory, directed by Vaidehi Jobanputra, PhD, FACMG, currently offers clinical exome sequencing for healthy individuals (Columbia Preventive Genomic Screen), diagnostic exome sequencing (CDEX, the Columbia Diagnostic Exome), cystic fibrosis screening and Sanger sequencing of individual variants. The latter test is crucial to our local precision medicine research initiatives because it ensures that high quality, clinical grade variant reports are transmitted to the electronic medical record, thereby translating laboratory-based precision medicine technologies into clinical decision-making tools. The PGL is committed to continuing to work with CUIMC physician scientists on identification and development of novel applications for high-throughput genomic sequencing, offering tremendous potential for maximizing the clinical utility of local precision medicine efforts.

In order to bridge the gap between laboratory medicine and patient care, the PGL employs a team of genetic counselors to act as liaison between clinical care providers and lab scientists. This interdisciplinary program ensures that clinical genomic results generated in PGL are used to inform and guide personalized, patient-focused healthcare for the CUIMC-NYP community.

The PGL has also been an integral part of the Columbia University Biobank (CUB) COVID-19 genomic profiling efforts at CUIMC. By performing DNA extraction from residual clinical specimens, the PGL, in partnership with the IGM, has supported the generation of over 1,000 exome sequences and single nucleotide polymorphism (SNP) profiles, which have been used by CUIMC researchers to further our understanding of the virus.

Laboratory of Personalized Genomic Medicine (PGM)

The Laboratory of Personalized Genomic Medicine (PGM) in the Department of Pathology and Cell Biology is a state-of-the-art diagnostic laboratory that performs cutting-edge tests in the areas of genetics, neurogenetics, oncology, cytogenomics, and molecular microbiology. The CLIA-accredited laboratory, directed by Mahesh Mansukhani, MD, is accredited by the College of American Pathologists (CAP), and the Clinical Laboratory Evaluation Program of the New York State Department of Health (NYS-DOH).

PGM offers multiple clinical molecular oncology and constitutional genomics assays, including single gene assays, small cancer panels, a large 467-gene cancer panel, as well as whole-transcriptome sequencing. In 2020, PGM performed over 45,000 clinical tests including over 6,000 constitutional genetics assays, nearly 5,000 oncology assays, and over 35,000 molecular microbiology and virology assays.

In recent years, the PGM has developed a national presence in the field of molecular oncology laboratory testing. In 2020-2021, PGM worked with the Herbert Irving Comprehensive Cancer Center (HICCC) to launch the Columbia Precision Oncology Initiative (CPOI), through which patients with priority cancer types received clinically-actionable DNA- and RNA-based genomic profiling. In 2022, PGM will work with the HICCC and Department of Pediatrics in the upcoming ComboMATCH and NCI-COG Pediatric MATCH clinical trials, which employ combinations of precision medicine agents to treat a variety of cancers in the pediatric and adult patient populations. This participation follows PGM's selection as an approved laboratory for the ongoing NCI-Molecular Analysis for Therapy Choice (NCI-MATCH) precision medicine trial. PGM has also partnered with Dr. Andrea Califano in the Department of Systems Biology to offer clinical Darwin

OncoTarget[TM]/OncoTreat[TM] analysis of transcriptomes, a powerful and novel systems biology approach that assesses activity of potentially targetable master regulators.

In addition, PGM has completed validation of an NGS assay for viral detection utilizing intellectual property developed in the Center for Infection and Immunity, Columbia University Mailman School of Public Health. The laboratory also has provisional New York State approval to confirm specific SARS-CoV-2 variants of interest. During the COVID-19 emergency, the laboratory of PGM completed verification of the first clinical SARS-CoV-2 test performed at the Medical Center, and an FDA emergency use authorization (EUA) was obtained by the PGM laboratory for a SARS-CoV-2 assay developed at the Center for Infection and Immunity of the Mailman School of Public Health.

PGM faculty and staff members participate in pediatric and adult molecular tumor boards at CUIMC and nationally in the American Society of Clinical Oncology's Targeted Agent and Profiling Utilization Registry (TAPUR) study molecular tumor board. Additionally, the PGM bioinformatics team, led by Dr. Susan Hsiao, has led CUIMC involvement in Project GENIE, an American Association for Cancer Research program for aggregation of cancer genomics and clinical outcome data in a HIPAA compliant registry with the goal of catalyzing clinical and translational cancer research. The laboratory has been a leading site demonstrating the value of optical genomic mapping in Leukemias and for other clinical conditions under the leadership of Dr. Brynn Levy. The Laboratory of Personalized Genomic Medicine is committed to supporting and enhancing clinical and research initiatives among the CUIMC precision oncology community.

Center for Precision Medicine and Genomics (CPMG)

The success of the CPMI requires a transformation of our clinical and translational paradigms and infrastructures. It also demands simultaneous, extensive education of healthcare providers on multiple levels. A collaboration between the Department of Medicine (DoM) and the Institute for Genomic Medicine (IGM), the Center for Precision Medicine and Genomics (CPMG) in the Department of Medicine brings together physicians, scientists, and other healthcare professionals to deliver the promise of Precision Medicine for adult constitutional disorders. Led by Dr. Ali Gharavi, MD, the Center builds on the existing collaborations between the DoM, the IGM, and virtually every clinical and basic science department at CUIMC. The Center develops a clinically oriented Precision Medicine program in each subspecialty of Internal Medicine and aims to facilitate the implementation of genetic testing into everyday healthcare. In addition, CPMG leads educational programs for healthcare providers and physician-scientists. The broad range of programs developed to date includes summer internships for undergraduate and medical students, bi-weekly genetics case studies in internal medicine series, monthly seminars by prominent scientists, and an annual CME course on genomic medicine for healthcare providers. CPMG's team has created a vibrant multidisciplinary research program and continues to develop bioinformatics tools that will enhance our capacity for Precision Medicine across the entire campus. For more information on these activities, please visit the CPMG website: http://www.columbiamedicine.org/cpmg/

Precision Oncology and Systems Biology (POSB) Program

Cancer therapies have traditionally been based on the tumor site, like breast cancer or lung cancer. More recently, researchers have found that cancers across tumor sites have common genetic mutations, and those mutations can be targeted with specific drugs.

Precision cancer medicine is a rapidly developing field that goes beyond studying cancer by tumor site, integrating genetic sequencing techniques and fundamental laboratory research to uncover a patient's specific tumor mutations and molecular composition in order to deliver more personalized treatment. In January 2021, the Herbert Irving Comprehensive Cancer Center (HICCC) will welcome Adam Bass, MD, a leading physician-scientist in the field of cancer genomics and gastrointestinal cancer, as the founding director of the

Center for Precision Cancer Medicine and director of gastrointestinal oncology. He also will serve on the faculty of the Columbia University Vagelos College of Physicians and Surgeons, as Irving Professor of Medicine in the Division of Hematology and Oncology.

Dr. Bass joins the Precision Oncology and Systems Biology (POSB) Research Program – one of four research programs supported by the HICCC. He will lead an actively growing program of physician-scientists working at the interface of cancer biology and the development of new cancer diagnostics and therapies. The new center will coalesce investigators across Columbia and NewYork-Presbyterian in a 360-degree approach, not only bringing discoveries from the lab to patients' bedsides, but also incorporating research in real time, allowing researchers to understand how cancer evolves and adapts in response to therapies. A key initiative within the center will to study how tumors adapt during treatment, building of data that researchers will use to further refine their understanding of cancer's defense mechanisms and develop new drugs and drug combinations to counteract them. Columbia's Department of Systems Biology, one of the leading programs in the country, will collaborate to apply its pioneering algorithms that process and interpret these complex data.

OpenFold

The Columbia Precision Medicine Initiative invests in infrastructure and is supporting OpenFold. Developed by Dr Mohammed AlQuraishi and colleagues at the Program for Mathematical genomics, directed by Dr Raul Rabadan, OpenFold is a world-wide, community-driven effort to build an open-source protein structure prediction system. This system will utilize the latest advances in machine learning developed by Columbia's scientists. Crucially, it will be built in a modular manner to serve as a platform for developing life science applications, similar to how software platforms enable numerous applications. Running at full capacity the initial cluster of 100 GPUs will enable training of a protein structure prediction system in one-to-two months of computing time and, subsequent to training, will predict ~6 protein structures per day.

Irving Institute for Cancer Dynamics (IICD)

The Herbert and Florence Irving Institute for Cancer Dynamics (IICD), directed by Simon Tavaré, was launched in July 2018. IICD is an interdisciplinary institute located on the Morningside Heights campus and focused on the interplay between STEM disciplines and cancer research. IICD collaborates across disciplinary boundaries to support research and develop technology that can improve our understanding of cancer biology, origins, evolution, treatment, relapse and prevention. The IICD is housed in newly renovated space in Schermerhorn Hall.

The Institute appointed its first endowed chair, Elham Azizi, Assistant Professor of Biomedical Engineering and Herbert and Florence Irving Assistant Professor of Cancer Data Research, in January 2020. Dr Azizi's research uses single-cell genomic technologies to study the heterogeneity in the tumor microenvironment and underlying mechanisms of response to immunotherapies in cancer patients. IICD also expanded its research themes by recruiting three Associate Research Scientists who will develop independent research projects: Dr David Tourigny (cancer metabolism), Dr Sanket Rane (immunology) and Dr Karol Nowicki-Osuch
(esophageal cancers), and recruited several Postdoctoral Research Scientists. The Institute also counts 14 Affiliates and Associate Members that are supporting the Institute's mission.

IICD is also developing a strong outreach program by providing seed grant funds and supporting working groups, summer internships and seminar series. During the fall, IICD partnered with the Probability and Society Initiative to invite two stellar speakers, Amaury Lambert (professor at Sorbonne Université in Paris) and Alison Etheridge (Professor of Probability and Head of the Department of Statistics, University of Oxford)
for a mini series of six virtual lectures on probabilistic modeling in biology.

IICD is also supporting instrumentation throughout the campus and NYC. The Institute partnered with the NYGC to build a Direct Library Preparation Plus+ (DLP+) device, a scalable single cell whole genome sequencing system. Additionally, IICD will build in the ZMBBI a serial two-photon tomography system, together with an automated collector, to image and annotate tumor biopsies. We built a Virtual Reality suite in
the IICD space that will allow tumors to be visualized in 3D when in-person research fully resumes. The Institute also supported the purchase of a 10X chromium system and a MiSeq DNA sequencer on the Morningside Heights campus, in partnership with the department of Biological Sciences.

Precision Medicine Awards

The annual Precision Medicine Pilot Grants have been awarded to five teams of researchers conducting innovative basic science, translational, and clinical research across multiple diseases. Jointly awarded by the Columbia Precision Medicine Initiative (CPMI), the Herbert Irving Comprehensive Cancer Center (HICCC), and the Irving Institute for Clinical and Translational Research (Irving Institute), the Precision Medicine Pilot Grants underscore Columbia's commitment to supporting diverse, cross-disciplinary research targeting the promise of precision medicine.

The five winning teams are being led by faculty at Columbia's Vagelos College of Physicians & Surgeons (VP&S), including: Srilaxmi Bearelly, MD, associate professor of ophthalmology; Brian Henick, MD, assistant professor of medicine; Chi-Min Ho, PhD, assistant professor of microbiology and immunology; Yufeng Shen, PhD, associate professor of systems biology and of biomedical informatics; and Xuebing Wu, PhD, assistant professor of systems biology and of medicine. The projects being funded are focusing on a range of research, from novel cancer therapeutics to health disparities research.

The Vagelos Precision Medicine Pilot Grant program is made possible by a generous donation from Roy and Diana Vagelos and is intended to support groundbreaking basic research in the field of precision medicine. Each research team receives $100,000 in funding for one year. The researchers will present their projects at an annual symposium for the precision medicine awards in fall 2022.
Award-winning teams:

Retinal Imaging and Deep Learning to Identify Maternal Risk & Reduce Racial Disparities
Lead Investigator: Srilaxmi Bearelly, MD
Co-Investigators: Ronald Wapner, MD and Andrew Laine, DSc
Pictures of the back of the eye help us to understand blood vessel changes in disease and health. One of the primary aims of this study is to understand if there are changes in blood vessels in the retina prior to the development of preeclampsia. Preeclampsia is a serious disease of pregnancy that can lead to morbidity and mortality and is more common among racial and ethnic minorities. There is an enormous unmet need to detect preeclampsia at early pre-clinical stages to prevent mortality. The retinal imaging (photo of the back of the eye), is a technique that is non-invasive, requires no dilation, and involves minimal risk to patients. It will be performed on 1,500 pregnant subjects. The goal is to tailor prenatal medical care (prevention, diagnosis, and ultimately treatment of this disease) to the individual patient.

Patient-Derived Organoids to Model and Manipulate Tumor Regulatory Dependencies in Esophageal Adenocarcinoma
Lead Investigator: Brian Henick, MD
Co-Investigators: Andrea Califano, Dr; Chao Lu, PhD; Hiroshi Nakagawa, MD
Patients with advanced/metastatic esophageal adenocarcinoma (EAC) suffer poor outcomes despite new drug approvals, perhaps because EAC actually represents multiple cancer subtypes not easily distinguishable with conventional techniques. Studying tumor RNA, the Califano laboratory has developed algorithms that can delineate EAC subtypes based on the differential activity of Master Regulator (MR) proteins that mechanistically govern tumor cells' transcriptional states, amenable to confirmation in model systems. Manipulating MRs genetically or with drugs identified by the CLIA-certified OncoTreat algorithm can help repurpose existing drugs for use in EAC subtypes on a case-by-case basis. Testing drug efficacy in tumor models by this approach could identify promising new therapies for multiple EAC subtypes simultaneously. Patient-derived organoids (PDOs) are an efficient model system that can recapitulate tumor biology and likelihood of treatment response. The team plans to confirm that human EAC share MRs with their derived PDOs in the Nakagawa laboratory. In the Lu laboratory, they will experimentally knock out MRs predicted to be most essential in each PDO, and finally test a library of drugs to identify those most likely to benefit each EAC subtype.

Direct Visualization of Malaria Parasite Invasion Using Cryoelectron Tomography
Lead Investigator: Chi-Min Ho, PhD
Co-Investigator: David Cobb, PhD
Half the world's population lives at risk of contracting malaria, which results in more than 400,000 deaths per year. Malaria is caused by malaria parasites that make us sick by invading and replicating inside our red blood cells. In order to enter human red blood cells, the malaria parasite, Plasmodium falciparum, assembles large protein complexes that bind to protein receptors displayed on the surface of the host red blood cell.

These large invasion complexes are essential for the parasite to be able to attach to and enter the red blood cell. The components of these invasion complexes are attractive targets for the development of new anti-malarial therapies and vaccines. Unfortunately, the complexes are short-lived, making them difficult to isolate for structural and functional studies. Drs. Ho and Cobb aim to overcome this obstacle by leveraging recent advances in in situ cryoelectron tomography to directly visualize the full invasion machinery in frozen samples of malaria parasites captured in the act of invading human red blood cells.

Develop New Computational Methods to Predict Functional Impact of Missense Variants Based on Protein Structure Using Machine Learning
Lead Investigator: Yufeng Shen, PhD
Co-Investigator: Mohammed AlQuraishi, PhD
Accurate and scalable interpretation of genomic variation is a critical component to realize the full potential of high-throughput sequencing in human genetics and genomic medicine. Missense variants account for most of protein-coding variants with potentially large functional impact; however, most of them do not contribute to disease. The inability to accurately predict their functional impact is a critical hurdle to identifying risk genes in genetic research studies. This project aims to develop new computational methods to predict functional impact of missense variants by leveraging the latest machine learning methods, protein structure, and large genome sequence data of diverse populations. The proposed methods will improve the utility of genome sequencing and enable new discoveries in genetic studies and clinical diagnosis.

A Special Ribosome in the Heart: Understanding how Mutations in Ribosomal Protein RPL3L Cause Neonatal Dilated Cardiomyopathy by Using Patient-derived iPSCs and Genetically Engineered Mice
Lead Investigator: Xuebing Wu, PhD
Co-Investigators: Steven Marx, MD; Teresa Lee, MD; Mythily Ganapathi, PhD
Mutations in genes can cause severe heart failure in infants. We do not yet fully understand which genes will cause infantile heart failure and what drives it. The research team recently discovered such mutations in RPL3L gene, which encodes a component of the ribosome, the machinery responsible for decoding genetic information and make proteins in every cell. Although initially we thought every human cell has the same ribosome, it turns out in heart and skeletal muscle cells, ribosomes are different from all other human cells as they replace another protein with RPL3L. This project will study the molecular and cellular mechanisms of the special ribosome by using patient-derived stem cells and genetically engineered mouse models. The project's aim is to help elucidate why heart and muscle cells require a special ribosome, and understand how the mutation causes infantile heart failure.

Mouse Genome Editing Awards

The Initiative supports awards for mouse genome editing with the objective of funding the generation of mouse models of human disease.

Awards for 2021:

Mouse models of Stargardt disease for hypomorphs and modifiers
Rando Allikmets, PhD and Takayuki Nagasaki, PhD; Department of Opthalmology
Disease-associated variation in the ABCA4 gene (population frequency 1:20) has emerged as the most prevalent cause of Mendelian retinal disease affecting at least 60,000 people in the United States. The extensive clinical heterogeneity of ABCA4/Stargardt disease, reflects its equally large genotypic profile with >1400 disease-associated variants. Comprehensive understanding of the genotype/phenotype correlations is necessary for diagnostic confirmation and essential for dissecting disease heterogeneity to improve designing therapeutic applications. In this study we are focusing on the late-onset disease, which accounts for ~40% of all patients and is caused by hypomorphic (i.e., "very mild" alleles with incomplete penetrance) variants. We have extensively investigated, including in knock-in mouse models, the two most common hypomorphic alleles of ABCA4, p.G1961E and p.N1868I. In this study, we expand the analysis for two more alleles, p.R2107H, which is the most frequent hypomorphic ABCA4 disease-associated variant in African Americans (MAF>20% in patients of African descent), and the p.G863A variant, which is a modifier and causes the disease if allelic with the p.N1868I variant. We have started to generate the two KI strains by CRISPR/Cas9. Once available and when we expand the colonies, we will analyze the strains by a pre-defined set of functional and imaging tests, including immunohistochemistry and electron microscopy to determine subcellular localization, electroretinogram, ATPase and substrate transport assays, and quantitative autofluorescence (qAF). The combined dataset will allow determining the disease onset, progression and pathogenetic mechanism for the two specific alleles and their combinations with other alleles.

Two different neurological diseases are caused by different mutations in the Pumilio1 gene

Vincenzo Genarrino, PhD; Department of Genetics & Development, Pediatrics and Neurology

Pumilio1 (PUM1) is a member of the Pumilio/fem3 mRNA-binding protein family (PUF) and is highly conserved in nearly all eukaryotic organisms. PUM1 primarily acts to repress nascent mRNAs via mRNA decay and translational inhibition, and has been implicated in development, stem cell fate, neurological functions and mRNA transport. We have identified over sixty patients bearing de novo or heritable pathogenic PUM1 variants and defined two novel neurological diseases: Pumilio1-Associated Developmental Delay and Seizures (PADDAS) and Pumilio1-related cerebellar ataxia (PRCA). There is a concordant severity in symptoms observed with Pum1 protein levels: PADDAS patients displaying milieu symptoms at earlier onset and have a 50% reduction, whereas PRCA patients present ataxia symptoms alone with a later onset and have only a 25% reduction. The most prevalent pathogenic variants etiological of these two conditions are Pum1-R1147W and Pum1-T1035S for PADDAS and PRCA, respectively. Since identifying and characterizing these diseases through clinical, molecular, and biochemical data, we have generated a Pum1-R1147W mouse model, made possible through funding provided by the department of Precision Medicine. These mice recapitulate disease phenotypes including developmental delay, motor dysfunction, hyperactivity, and seizures. We are currently in the process of acquiring Pum1-T1035S mice through funds provided by the Precision Medicine RFPs. Through the study of these two variants, we will be able to expand our knowledge of these disease mechanisms, identify druggable targets for gene and pharmacological therapies, and contribute to a greater understanding of Pum1 in the brain.

Generation of mouse models of schizophrenia risk mutations in the SETD1A gene

Joseph Gogos, MD, PhD; Professor of Physiology and Cellular Biophysics, Neuroscience and Psychiatry (in the Mortimer B. Zuckerman Mind Brain Behavior Institute)

We have previously linked risk of schizophrenia to loss-of-function mutations in SETD1A, a lysine methyltransferase involved in chromatin regulation. This finding was subsequently confirmed by large-scale exome sequencing studies and meta-analyses. SETD1A is not only a confirmed schizophrenia risk gene but loss-of-function mutations in SETD1A show the strongest statistical support to date for association with schizophrenia. Moreover, SETD1A mutations confer a large increase in disease risk thus providing an excellent genetic substrate for disease modeling. The nature of phenotypic heterogeneity across patients with schizophrenia remains unclear. Notably, gene-disrupting de novo mutations affecting the same gene often result in substantially different phenotypes depending on the exon where a gene disrupting mutation resides. To characterize in detail the phenotypic heterogeneity associated with SETD1A mutations we are developing by means of the CRISPR-Cas9 system a set of mice engineered to carry two distinct risk alleles in the same genetic background: a mutation that creates an early stop codon and leads to a predicted protein truncation and a de novo indel changing the canonical splice acceptor site predicted to lead to loss of exon 16 and disruption of histone methyltransferase activity. Notably our results will be compared to parallel analysis of existing isogenic human iPSC lines carrying identical gene disrupting SCZ-linked mutations. We expect that our work will provide valuable mechanistic insights and identify novel drug targets, tailored to the effects of individual risk mutations.

Murine models of FHOD3 mutations causing hypertropic and dilated cardiomyopathy

John P. Morrow, MD; Department of Medicine; Gregg G. Gundersen, PhD; Howard J. Worman, MD; Pathology and Cell Biology

In a collaborative effort, the laboratories of Morrow, Gundersen and Worman have recently shown that cardiomyocytes from the hearts of mice with a cardiomyopathy-causing Lmna (lamin A/C) mutation have abnormal positioning of nuclei. This is due to inactivation of the protein FHOD3. FHOD proteins play critical roles in transducing forces from the cytoplasm to the nucleus. As a result of this abnormal nuclear positioning, we have hypothesized that cardiomyocytes suffer nuclear envelope rupture, DNA damage, and defects in sarcomere function. Human genetics shows that mutations in FHOD3 account for 2-4% of monogenic cardiomyopathy cases, on par with individual genes for sarcomeric proteins. However, FHOD3 mutations are unique in that they are a major cause of both dilated and hypertrophic cardiomyopathy. We hypothesize that FHOD3 mutations inactivate its ability to mediate proper nuclear positioning in cardiomyocytes, leading to a cascade of pathogenic events. To test this hypothesis, we propose to a novel mouse knock-in model with a Fhod3 mutation that causes cardiomyopathy in humans. In addition to allowing us to test our novel hypothesis on the pathogenesis of cardiomyopathy, these mice will be the first available animal models for human cardiomyopathies caused by FHOD3 mutations. Overall, this research could lead to precision medicine approaches to treat genetic hypertrophic and dilated cardiomyopathies.

Mouse model to establish the role of ARNT2 in the weight regulation pathway
Vidhu Thaker, MD; Department of Pediatrics
The leptin melanocortin pathway is the primary known regulator of energy homeostasis and body weight. Many genes that play an important role in this pathway have been identified as monogenic cause of obesity in both human and murine studies. A key regulatory transcription factor in this pathway is Single-minded 1 (SIM1), a basic helix-loop-helix/PER-ARNT-SIM (bHLH/PAS) transcription factor involved in the development and function of the paraventricular nucleus of the hypothalamus (PVH), a region critical for energy homeostasis. Haploinsufficiency of SIM1 causes early-onset obesity in humans as well as animal models. In human studies, we have identified a novel de novo variant in in Aryl hydrocarbon receptor nuclear translocator 2 (ARNT2) in an adolescent with severe early onset obesity. As ARNT2 is an obligate heterodimer of SIM1, we hypothesize that loss of function of ARNT2 will have a phenotype similar to that seen with the loss of SIM1 in animal models. In this proposal, we aim to generate a mouse with the patient specific mutation to allow us to study the molecular perturbations that result in obesity. We will use the mouse model to confirm our hypothesis on the impacted pathways with the loss of dimerization. Based on the currently known biological function of SIM1/ARNT2 complex, we also expect to assess two currently available therapeutic strategies on the mouse model as proof of principle for use of such modalities in humans in future.

Precision SNP therapeutic Editing for Autosomal Dominant Retinitis Pigmentosa
Stephen Tsang, MD, PhD; Department of Ophthalmology
In the U.S., approximately one quarter of all autosomal dominant retinitis pigmentosa (adRP) cases are caused by mutations in the gene RHO, which encodes the primary light-sensing protein rhodopsin (RHO). Any one of the 150 mutations in RHO blind nearly 10,000 Americans. Although many CRISPR-based therapeutic genome surgery approaches focus on a mutation-specific gene repair strategy, our goal here is to create a more generalizable approach. Without a universal strategy, more than 150 different gRNAs and respective clinical trials would be required to account for all the mutations found in RHO.5 Because our CRISPR editing strategy is targeting the human-specific sequences, which do not exist in the currently available knock-in Rho-adRP murine lines,6-8 a novel humanized RHO adRP mouse model is required. Thus, if AAV: Cas9 and AAV:human-sgRNAs can repair the RHOP347Lallele in humanized mice, the two AAV gene-editing vectors could be immediately redeployed for clinical trials without further modifications.

Precision Medicine and Society

In the past year, Columbia faculty have continued to explore the impact of precision medicine on diverse fields, including economics, law, the humanities, and sociology as part of Columbia's Precision Medicine and Society (PM&S) program within the University's overall Precision Medicine Initiative. The program is directed by a Steering Committee of faculty chaired by Paul Appelbaum, MD and Gil Eyal, PhD.

Precision Medicine: Ethics, Politics and Culture (PMEPC)

Sponsored by the PM&S program, PMEPC funds graduate fellowships and a series of scholarly events. During the 2020-21 academic year, Maya Sabatello, LLB, PhD and Dr. Eyal invited five scholars to give public lectures and hold workshops with PMEPC fellows on topics ranging from gene therapies for children to the use of race and ethnicity within the field of genomics in light of racial reckoning in the United States. Given the Covid-19 pandemic, all events were held remotely.

Drs. Sabatello and Eyal continue to co-lead the series in 2021-22. The public lectures for this year will include Jennifer Young, PhD, on Asian Americans in genetic healthcare and research; Aviad Raz, PhD, on communication of uncertainty in genomic cancer care; Jada Benn Torres, PhD, on race and genetic identities; and Hila Lifshitz-Assaf, MBA, DBA, on Artificial Intelligence (AI) algorithms in medical decision making. You can find details on the series, including the dates of the 2021-22 events [here.](here)

In the 2020-21 program, the PMEPC sponsored eight Graduate Fellows. All of the Fellows are participating in our series of public talks and small group meetings. The 2020-21 Fellows were:

- Colby Lewis (Biostatistics)
- Bella Horton (Sociomedical Sciences)
- Sarah Adelman (Population and Family Health)
- Lulu Chen (Medicine)
- Bree Martin (Genetic Counseling)
- Ari Gaiper (Sociology)
- Clare Casey (Anthropology)
- Supriya Kapur (Sociomedical Science)

As part of the Fellowship, one of the fellows, Supriya L. Kapur, has published an article on AI bias and genomics. Other fellows and our Graduate Assistant have submitted or are in the process of submitting manuscripts for review.

We have recently circulated a call for the 2021-22 PMEPC Graduate Fellowships. As was the case last year, each of new Graduate Fellows will develop a publishable research paper relating to PM&S.

This combination of public talks, working group discussions and publications will encourage extensive engagement in PM&S issues among students in the upcoming year.

PM&S Publications

The members of the PM&S Steering Committee collaborated on a paper considering the implications of precision medicine in the Covid-19 pandemic (published in *Genetics in Medicine*). Research conducted with PM&S funding resulted in a study on teenagers in precision psychiatry published in *Public Health Genomics,* and another on the potentially negative impacts of polygenic scores for educational attainment appearing in *Social Psychology of Education*. Members of the Steering Committee also published articles addressing:

- Stigma from genetic research in South Africa;
- The impact of genetic testing for cardiomyopathy in adolescents;
- The behavioral effects of personalized genetic information on marijuana and schizophrenia risk;
- Legal requirements for the return of reinterpreted genetic test results;
- Economic and population health challenges of genetic variant reinterpretation;

- Screening for genetic literacy;
- Perspectives of deaf/hard of hearing individuals on precision medicine research;
- The use of behavioral genetics in schools;
- The impact of psychiatric genetics on child custody proceedings; and
- The dynamics of claiming in an online "long haul" covid-19 community.

These publications can be found [here.](#)

Precision Medicine & Society Events

Center for Research on Ethical, Legal & Social Implications of Psychiatric, Neurologic & Behavioral Genetics

During the 2020-21 academic year, the Center hosted nine scholarly presentations. Presenters included:

- Victor Penchaszade, MD, MSPH, Graduate Program in Genetics, Human Rights and Society, Universidad Nacional de Tres de Febrero, Buenos Aires, Argentina
- Ilina Singh, PhD, Departments of Psychiatry and Neuroscience, University of Oxford, UK
- Kimberly Kaphingst, ScD, Department of Communication, University of Utah
- Ruth Landau, PhD, School of Social Work and Social Welfare, The Hebrew University of Jerusalem, Israel
- Kostas Kampourakis, PhD, Section of Biology, University of Geneva, Switzerland
- Susan Domchek, MD, Basser Center for BRCA, University of Pennsylvania
- Steven Joffe, MD, Departments of Medical Ethics & Health Policy and Pediatrics, University of Pennsylvania
- David Veenstra, PhD, School of Pharmacy, University of Washington
- Daniel Geschwind, MD, Department of Neurology, UCLA
- Bettina Meiser, PhD, Psychosocial Research Group, University of New South Wales, Sydney, Australia

Presentations planned for the 2021-22 academic year include:

- Daniel Navon, Ph.D., Department of Sociology, University of California, San Diego (Sept. 13, 2021)
- Shirley Sun, PhD, School of Social Sciences, Nanyang Technical University, Singapore (Oct. 25, 2021)
- Tania Simoncelli, MS, Vice President, Chan Zuckerberg Initiative (Nov. 15, 2021)
- Tim Yu, MD, PhD, Department of Pediatrics, Harvard Medical School (Dec. 16, 2021 (Note this seminar will take place on Thursday, 4-5 pm.)
- Danton Char, MD, Department of Anesthesiology, Stanford University (Jan. 24, 2022)
- Shawneequa Callier, JD, MA, Department of Clinical Research and Leadership, George Washington University (Feb. 14, 2022)
- Kathryn Phillips, PhD, Department of Clinical Pharmacy, University of California, San Francisco (Mar. 14, 2022)
- Ben Berkman, JD, MPH, Department of Bioethics, National Institutes of Health (Apr. 11, 2022)
- Susan Gelman, PhD, Department of Psychology, University of Michigan (May 16, 2022)
- Nathaniel Comfort, PhD, Department of the History of Medicine, Johns Hopkins University (June 13, 2022)

All talks will take place online during 2021-22, 12:00 - 1:00pm. To receive a link to each talk, interested individuals should send an email to janee.frankel@nyspi.columbia.edu.

PM&S Seminars and Conferences

Following successful conferences in April 2019 on Precision Medicine: Its Impact on Patients, Providers and Public Health and in May 2020 on Precision Medicine & Society: International Perspectives, we held our third annual conference in May 2021 on Precision Medicine & Society: New Perspectives. The conference highlighted the work of younger scholars in the field. Two themes were selected to capture exciting cutting-edge research that is being conducted by emerging scholars and that is pertinent to the key concerns of PM&S. One set of issues related to the promise of Machine Learning (ML) and AI to provide more precise

predictive models capable of improving, individualizing and perhaps even equalizing medical diagnosis, treatment and care. Another set of issues related to the ethical questions raised by genomics research, from the inclusion of underserved populations among research cohorts, to the problems encountered when extending precision medicine methods to the fields of psychiatry and socio-genomics. You can view the program, including the names and biographies of the speakers here, and recordings of each panel from the 2021 conference here.

In addition, in October 2020, the PM&S program hosted a virtual seminar covering the topic: Is Precision Medicine Relevant in the Age of Covid-19? The four speakers were Dr. Scott Gottleib, former Comissioner of the FDA; Dr. Teri Manolio, Director of Genomic Medicine at NHGRI; Professor James Heath, President of the Institute for Systems Biology; and Dr. Amy Zhou, Assistant Professor in the Department of Sociology, Barnard College. The seminar was moderated by John Rowe from the Mailman School of Public Health. You may view the seminar program, including the biographies of the speakers here, and the recording of the seminar in our video library here.

PM&S Seed Grants

During 2020-21, the PM&S program solicited applications jointly with the Center for Research on Ethical, Legal & Social Implications of Psychiatric, Neurologic & Behavioral Genetics for two rounds of seed grants to support research on the social, legal, political and ethical dimensions of precision medicine. A sub-committee of the Steering Committee reviewed the applications and selected two to be funded in each round. In the fall of 2020, funded projects focused on parental perspectives of genomic sequencing in newborn screening and on the diagnostics, identity, and geneticization of sexual behavior.

In the spring of 2021, projects were funded that addressed the different meanings given to precision medicine in grant proposals to the NIH, and the impact of polygenic prediction of education on public perceptions of educational, criminal, and life-long trajectories.

Intersectionalities in a Sociogenomic World: Does polygenic prediction of education impact public perceptions of educational, criminal, and life-long trajectories?
Lucas Matthews, PhD; Assistant Professor of Clinical Bioethics (in Psychiatry)

Imprecision and the different meanings of Precision Medicine
Larry Au, M.Sc; Ph.D. candidate in sociology

Educational Initiatives

One of the goals of the Initiative is to promote Precision Medicine education at all levels. There are currently opportunities to learn about precision medicine for graduate students: Wendy Chung developed and teaches a course on precision medicine to medical students, and Bhaven Sampat has developed and taught a class on precision medicine and economics.

We asked Drs. Rachel Adams (English), Gil Eyal (Sociology) and Sam Sternberg (Biochemistry) to create and teach a new undergraduate course for the Fall 2022 semester. The syllabus will cover the scientific foundations of precision medicine, its social dimensions, alongside fundamental humanistic questions and challenges raised by this discipline. It is designed as an introduction to precision medicine, particularly for the non-scientist student, but will also explore issues relevant to students who are planning a career in science or medicine.