

COLUMBIA PRECISION MEDICINE INITIATIVE

# 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. We are delighted to welcome Dean Katrina Armstrong, a strong supporter of precision medicine at Columbia.

Several months ago, Dr. Armstrong asked a task force of faculty from the Vagelos College of Physicians and Surgeons to develop priorities and plans for advancing the equitable implementation of genomic medicine at Columbia. Their recommendations focused on building on the impact of precision medicine at Columbia, creating a genomic medicine steering committee led by a chief clinical genomics officer, and integrating genomics into education throughout the health professions. Their report can be found [here](#).

We are also delighted to welcome Professor Hashim Al-Hashimi to the Department of Biochemistry and Molecular Biophysics at the Vagelos College of Physicians and Surgeons. Dr. Al-Hashimi pioneered the development and application of NMR and other biophysical approaches for visualizing how the three-dimensional structures of DNA and RNA molecules change with time at the atomic level. He also pioneered approaches for identifying RNA-targeting therapeutics using RNA dynamics. The appointment was made possible by financial support from the Diana and Roy Vagelos Precision Medicine Fund.

One of the goals of CPMI is to promote Precision Medicine education at all levels. We asked Professors Rachel Adams (English), Gil Eyal (Sociology) and Sam Sternberg (Biochemistry) to create and teach a new undergraduate course for Fall 2022. They developed the syllabus and taught the first course entitled "Precision Medicine: Ethical, biological and societal implications" in Fall 2022. In addition to covering the science that is the basis of precision medicine, the course included fundamental humanistic questions and challenges raised by this discipline. Course reviews were excellent. For academic year 2023/2024, the course will be offered in the Spring semester.

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

The Precision Medicine and Society program sets Columbia apart from other precision medicine initiatives by focusing on ethical and equity issues in the impact of precision medicine. This year we welcome Professor Rebecca Jordan-Young, who will join Paul Appelbaum as co-chair of the Leadership group. We thank Gil Eyal who previously served as co-chair with Paul for his excellent contributions. Gil will continue to be a member of the group. We continue to thank Paul for his commitment and service to this program.

Our sixth academic conference, Advances in Precision Medicine: Innovation, 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 seventh conference on May 19th, 2023, which will focus on chromatin and nuclear architecture 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 Maniatis, Ph.D.  
Director of Columbia University Precision Medicine Initiative;  
Isidore S. Edelman Professor in the Department of Biochemistry & Molecular Biophysics

# Advances in Precision Medicine Conference: Genomic Innovation & Precision Medicine: Reading, Imaging, Editing, and Writing the Genome

A key objective of the 6th annual conference was to provide an up-to-date perspective on the impact of genomic technologies on understanding the functional consequences of disease-associated DNA sequence variation on cellular and organismic function. For example, technologies that simultaneously interrogate RNA transcription, chromatin modification and chromosome structure in individual cells (multi-omics) are making it possible to probe deeply into the functional consequences of DNA sequence variation that associates with disease (at single cell, and single molecule, and atomic resolution). International leaders in the development and application of these technologies will come together to discuss progress and challenges.

Speakers included:

Jay Shendure, MD, PhD, University of Washington  
Rahul Satija, PhD, New York Genome Center  
Joakim Lundeberg, PhD, KTH Royal Institute of Technology  
Xiaowei Zhuang, PhD, Harvard University  
Ed Boyden, PhD, Massachusetts Institute of Technology  
Feng Zhang, PhD, Massachusetts Institute of Technology  
Jef Boeke, PhD, NYU Langone Health  
Tuuli Lappalainen, PhD, New York Genome Center  
Olga Troyanskaya, PhD, Princeton University; Flatiron Institute  
George Church, PhD, Harvard Medical School, Blavatnik Institute

Recordings of the talks can be found in our [video library here](#).

**SAVE THE DATE**

COLUMBIA PRECISION MEDICINE INITIATIVE  
ADVANCES IN PRECISION MEDICINE  
**CHROMATIN AND NUCLEAR  
ARCHITECTURE**

**SEVENTH ANNUAL CONFERENCE**  
MAY 19, 2023. 9:00am - 5:00pm

[Register Today!](#)

# Faculty Announcements

## Hashim M. Al-Hashimi, PhD



Dr. Hashim M. Al-Hashimi is a Professor of Biochemistry and Molecular Biophysics at the Columbia University Irving Medical Center. He was born in Beirut, Lebanon, and grew up in Greece, Italy, Jordan, and the UK. Dr. Al-Hashimi received his Ph.D. in Biophysical Chemistry from Yale University in 2000. There, he developed NMR spectroscopic methods to study the structure and dynamics of proteins. Between 2000 and 2002, Dr. Al-Hashimi was a postdoctoral fellow at the Memorial Sloan-Kettering Cancer Center in New York City, where he turned his attention toward studying the structural dynamics of nucleic acids. A year into his postdoctoral training, Dr. Al-Hashimi accepted an offer to join the faculty at the University of

Michigan. There he rose through the ranks and, seven years later, was named the Robert L Kuczkowski Professor of Chemistry and Biophysics. In 2014, Dr. Al-Hashimi joined the faculty at the Duke University School of Medicine, where he was the James B. Duke Professor of Biochemistry and Chemistry and Director of the Duke Center for RNA Biology. He joined the Columbia faculty on May 1, 2022. As a principal investigator, Dr. Al-Hashimi and his trainees pioneered the development and application of NMR and other biophysical approaches for visualizing how the three-dimensional structures of DNA and RNA molecules change with time at the atomic level. These technological advances resulted in a deeper and more quantitative understanding of many fundamental cellular processes, including the mechanisms of cancer-causing mutations and gene regulation by non-coding RNAs. Dr. Al-Hashimi also pioneered approaches for identifying RNA-targeting therapeutics using RNA dynamics, and in 2009, he co-founded Nymirum Inc to enable RNA-targeted drug discovery. He is the recipient of the Vilcek Prize for Creative Promise in Biomedical Science, the Founder's Medal in NMR Spectroscopy, the Agilent Thought Leader Award, and the National Academy of Sciences Award in Molecular Biology. He is a Fellow of the Biophysical Society and the International Society of Magnetic Resonance. Popular Science Magazine listed Dr. Al-Hashimi among the 'Brilliant 10' scientists and engineers in the USA. The appointment was made possible by financial support from the Diana and Roy Vagelos Precision Medicine Fund.

## UPDATES

### Institute for Genomic Medicine

Over the past year, the Institute for Genomic Medicine (IGM) and the Center for Precision Medicine and Genomics (CPMG), both under the leadership of Dr. Ali Gharavi, have continued to empower Precision Medicine across the medical center.

**The All of Us Program:** The IGM is the home of the All of Us program, the National Precision Medicine initiative. To date, over 35,000 participants from New York City have been enrolled into the study. Nearly 85% of participants are categorized as under-represented in biomedical research, indicating that the IGM is succeeding in its mission to engage diverse communities in genomics research. This national study provides genome sequencing and has now embarked on returning genetic results, which will enable genomic risk profiling for participants and family members. This effort will simultaneously engage Columbia providers in genomic practice. Finally, genomic data are now available from over 300,00 participants, enabling genomics research on a large scale.

**New Core Services:** In response to demand for more analytic and bioinformatics support for investigators, the IGM has expanded its core services for the Columbia community. New core services include genome sequence processing and annotation, diagnostic analysis for monogenic disorders, case-control association studies, and consultation for designing execution of genetic studies. Additional services include genetic counseling, return of genetic results, and assistance with establishment of

genetics clinics in medical subspecialties. The IGM team will also perform look-ups for variants and genes of interest in the IGM sequence database and other datasets such as the All of Us or UK biobank data repositories.

IGM researchers have also been active in the laboratory:

A collaboration between the **Kirylyuk and the Gharavi labs** has resulted in upcoming publications in Nature Communications and Nature Genetics, describing the genetic basis of variation in serum immunoglobulin A levels and genetic susceptibility to IgA nephropathy, one of the most common causes of kidney failure worldwide. Their genetic studies now enable risk stratification and prediction of patients at highest risk of progression to kidney failure. These studies have also identified a host of potential new drug targets for therapeutic interventions.

The **Gelinas lab** has been actively investigating neural circuit mechanisms of epilepsy and memory, as well as collaborating to translate novel bioelectronic devices to clinical applications. This work has led to multiple publications (PNAS, Science Advances, Brain, Nature Biomedical Engineering, eLife, Advanced Science, Nature Materials, or Cell Reports) and garnered extramural funding from NIH and NSF. Dr. Gelinas has also received the Taking Flight Award, through the CURE Foundation, and is a Louis V. Gerstner Jr. Scholar. She has been invited to present at the Presidential Symposium at the American Epilepsy Society meeting and at the Gordon Research Conference (Mechanisms of Epilepsy and Neuronal Synchronization).

The **Makinson Lab** has set up experimental systems including acoustoptic multiphoton imaging and establishing human cell models of neurodevelopmental disorders to better understand neurodevelopmental impairment in autism and epilepsy and to test novel gene therapy strategies. Dr. Makinson was awarded the prestigious NIH Director's New Innovator Award (DP2) to develop novel circuit models of the developing human brain using human brain organoids for studying neurodevelopment and neurodevelopmental disorders. Dr. Makinson published a manuscript in Nature Communications with Yueqing Peng in the IGM characterizing a sleep regulating circuit in the hypothalamus and he has a manuscript accepted at Nature Methods describing a novel genetically encoded voltage indicator. Dr. Makinson was also invited to give a talk on precision medicine strategies for treating SCN8A disorder at the American Epilepsy Society (AES) meeting and he was selected to serve on the Research and Training Council of AES for the next three years.

The **Peng lab** has been investigating the cellular and molecular mechanisms underlying sleep regulation in both normal and diseased brain. In 2022, Dr. Peng was awarded one NIH R01 and two R21 awards to investigate the role sleep and sleep circuits in neurologic disorders. Projects aim to dissect the neural circuits that control Non-REM sleep seizures and broaden our understanding of the reciprocal relationship between sleep and neurodegenerative diseases. IGM colleagues Makinson and Peng published a manuscript in Nature Communications characterizing a sleep regulating circuit in the hypothalamus. Dr. Peng also had a publication in iScience describing absence seizures in a mouse model of Gnb1 encephalopathy.

## Irving Institute for Clinical and Translational Research

In the past year under the leadership of Wendy Chung, MD, PhD, Krzysztof Kirylyuk, MD, Ronald Wapner, MD, and Gary Miller, PhD, 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, 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 (2022 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 30, 2022, research accomplishments of past and current pilot award recipients were celebrated at the annual symposium "Precision Medicine Scholars Day", hosted in-person 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 sixth 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 eighth 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 the Medical Center's first centralized resource of biospecimens linked with health data from the EMR. CUB activities were accelerated during the pandemic to enable COVID-related research at CUIMC; 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).

In 2022, CUB shifted its focus to a post-COVID environment with the development and implementation of large-scale recruitment and sample collection methods to support a wide range of strategic research priorities at the Medical Center. CUB has put in place an Epic order which allows for collection of CUB specimens at the time of a patient's routine clinical draws, and an e-consent tool that supports broad enrollment of patients with minimal coordinator effort. 2023 will see further expansion of the CUB's clinical partnerships, which currently include the Department of Emergency Medicine, Div. of Nephrology, Div. of Cardiology, Department of Pediatrics, and the Herbert Irving Comprehensive Cancer Center.

With support from Dr. Muredach Reilly and the Irving Institute for Clinical and Translational Research, the CUB has consented more than 4,000 patients for collection of biological samples, access to electronic health records, re-contact for participation in additional research studies, replenishment of depleted samples, banking of clinical residual samples, genomic research, and return of results. A long-term goal of the CUB is to offer participation to every patient of CUIMC-NYP.

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 is in the process of implementing a multidimensional 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.

Established in Fall 2022, the CUB Community Advisory Board (CAB) is comprised of community leaders and community health workers from local organizations based in Northern Manhattan, including the Northern Manhattan Perinatal Partnership, Dominican Women's Development Center, Northern Manhattan Immigrant Coalition, Mexican Coalition, and the Community League of the Heights. The goal of the CAB is to further transparency and awareness of CUB activities with the members of the Northern Manhattan Community. The first meeting of the CUB CAB is scheduled for February 2023, with additional instances set to take place later in the year.

## 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)

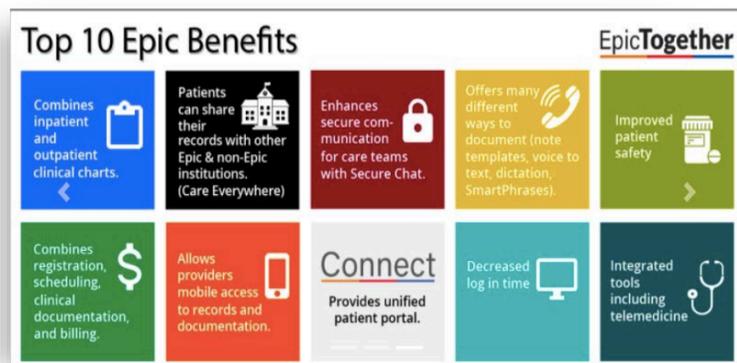
The Targeted Research and Exploration Advancing Trial Models, Editing, and Next-generation Therapies (TREATMENT) program was established by Dr. Wendy Chung to expand our capacity to care for patients with rare genetic diseases, understand the natural history and molecular mechanisms of genetic diseases, 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. One of our N of 1 treatments was recently featured in the New York Times (<https://www.nytimes.com/2022/12/19/health/rare-disease-genetic-treatments.html>). 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, Fabry disease, NGLY1 deficiency, 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-lead in this phase by investigators Chunhua Weng, PhD, Wendy Chung, MD, PhD, George Hripcsak, MD, Krzysztof Kiryluk, MD 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 and Spinal Muscular Atrophy screening and Sanger sequencing of individual variants to confirm the findings from research projects and familial variant testing. 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 exome and genome sequencing, 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 for solid tumors and myeloid neoplasms, a large 568-gene cancer panel, cancer whole exome as well as whole-transcriptome sequencing. In 2022, PGM performed nearly 55,000 clinical tests including over 3,000 constitutional genetics assays, nearly 5,000 oncology assays, and over 44,000 molecular microbiology and virology assays.

In recent years, the PGM has developed a national presence in the field of molecular oncology laboratory testing. In 2022, PGM launched its new 568 gene comprehensive cancer profiling assay, developed with the GOAL (Genomic Organization for Academic Laboratories). The assay tests normal DNA, and tumor DNA and RNA and detects sequence variants, genomic rearrangements, RNA fusions, copy number alterations, tumor mutation burden and microsatellite instability. The laboratory received New York State approval for a circulating tumor DNA (ctDNA) assay, and for a new PCR-based microsatellite instability test with a lower minimum tumor percentage. It has also completed validation of digital PCR for sensitive quantification of BCR-ABL1 p190 transcripts to monitor residual disease in Philadelphia Chromosome-positive Acute Lymphocytic Leukemia.

In 2022, PGM started transitioning to a true Laboratory Information system for its entire workflow. In addition to EPIC integration, automated tracking of the entire testing process, and reduction of the risk of error, PGM is leveraging the capabilities of this system to transmit discrete data to the EPIC – both for numeric results such as BCR-ABL1 transcript levels, and direct reporting of genomic variants to the EPIC genomics module. The lab – under the leadership of Dr. Susan Hsiao - has completed all bioinformatics and IT processes for automatic transmission of appropriately formatted results of the Myeloid panel to the EPIC genomics module, and awaits its initiation by the EPIC team.

In 2023, PGM will continue to 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™/ OncoTreat™ analysis of transcriptomes, a powerful and novel systems biology approach that assesses activity of potentially targetable master regulators. PGM is also working actively in a cross-campus initiative with our colleagues at Weill-Cornell to standardize molecular oncology testing across both campuses to meet the testing needs of our cancer patients and clinical investigators.

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. In 2022, PGM validated and obtained New York State approval for a non-variola Orthopoxvirus test to support the needs of NYPH for rapid results, when reference laboratories were overwhelmed and unable to meet the system's turnaround time needs.

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)

CPMG aims to build highly collaborative networks that bring together physicians, scientists, and other healthcare professionals to accelerate the implementation of Precision Medicine in clinical care for adult constitutional disorders.

CPMG ongoing research involves studies of underrepresented populations and health disparities in genomic medicine. Dr. Maya Sabatello's program is investigating the inclusion of people with disability in Precision Medicine research and intersectionality, the return of genetic results from research, and the relationship between big data, bias and equity. In a 2022 publication in *Science*, Dr. Sabatello discussed data sharing and community-engaged research.



In another publication in the *Am J Hum Genet*, Dr. Sabatello and colleagues also discussed how to remedy underrepresentation in genomics research through community engagement. Dr. Sabatello also presented her research at the NICHD strategic planning (2021), NHGRI Future Directions (2022), NHGRI Disability Symposium (2022) meetings. Her work has been recognized by five NIH R01 awards in the past two years.

In the past year, CPMG has successfully developed genetics clinics across the Department of Medicine (in the Nephrology, Hepatology, Hematology and Pulmonology Divisions), highlighting the growing demand for clinical genetics. CPMG's genetic counselors (GCs) have analyzed more than 400 cases, and about a third of them were discussed at multidisciplinary genetic sign-out meetings that are attended by GCs, researchers, and clinicians. CPMG researchers described their experience in initiating a kidney genetics clinic in a 2022 publication in the *American Journal of Medical Genetics Part C*.

To promote the understanding and adoption of Precision Medicine concepts and services, CPMG offers a broad range of seminar series and CME programs, including "*Genetic Case Study in Internal Medicine*" (a biweekly CME series that focuses on the application of genetics in the clinical setting), and "*CME courses on Medical Genetics for Internal Medicine*"; (streaming platform courses attended by hundreds of participants across the country). Three CME courses were offered in 2022 ("Genetics for Internists", "Genetics for Nephrologists", "Genetics for Hepatologists"). The "Genetics for Nephrologists" course counted over 700 registrants.

CPMG continues to offer training to undergraduate students during the academic year and summer, fostering student interest in genetic research and supporting future genetic community.

To bring equity and opportunity to all New York students, CPMG partnered with the LifeSci NYC initiative to enhance participation of underrepresented minorities in the summer programs.

Building on its success in implementation of Precision Medicine, CPMG received a NIH award aiming to return genetic results to participants in the CureGlomerulopathy network, a national study of 2400 individuals with primary glomerular disorders. This study is expected to set standards for return of genomic results to research participants on a national scale. CPMG investigators also designed a large national study sponsored by Natera, aiming to test the impact of genetic testing on kidney disease management. This multicenter study has successfully recruited over 1700 individuals in the United States, and preliminary results will be presented at the 2023 National Kidney Foundation meeting.

## Precision Oncology and Systems Biology (POSB) Program

The POSB program, within HICCC, represents a highly novel, leading effort to combine cutting-edge systems biology approaches and translational expertise to develop mechanism-based, biomarker supported clinical trials. Cancer therapies have traditionally been based on the tumor site. More recently, however, researchers have found that cancers across tumor sites present a large number of common dependencies, including in mutated oncoproteins and in master regulator proteins that are not mutated but are responsible for integrating the effect of mutations in their upstream pathways. Similarly, our improved understanding of tumor heterogeneity—largely due to advances in both single cell profiling and in the analytical approaches to analyze the resulting data—has identified tumor heterogeneity as perhaps the most critical contributor to the emergence of drug resistance. To address these challenges, the POSB program is leveraging multi-omics profiling and systems biology-based modeling of cancer cells to identify and target pharmacologically accessible oncogene and non-oncogene tumor dependencies, especially within single cell subpopulations that co-exist in the same tumor mass but present complementary drug sensitivity. Additionally, the program is critically involved in the elucidation of tumor-related mechanisms that can be leveraged to produce accurate and highly robust biomarkers, especially using radiomics and virtual proteomics-based approaches.

These directions have led to numerous investigator initiated clinical trials (through the HICCC clinical protocols and data management office) that have produced elucidation of predictions, ranging from the use of selinexor in GBM - perhaps the only study producing a significant signal in this devastating disease in the last 30 years, and ricolinostat in metastatic breast cancer, based on the activity of its high-affinity target HDAC6 in patients. These papers can be found on our website [here](#).

Among the key initiatives within the POSB program are the study of tumor adaptation during treatment, the use of computationally predicted drugs in basket studies, such as the recently launched HIPPOCRATES study in pancreatic ductal adenocarcinoma, and the use of single cell technologies and network biology to elucidate druggable dependencies both in tumor subpopulations as well as in the tumor microenvironment.

The Co-Leaders of the POSB Program are: Andrea Califano, Dr; Ken Olive, PhD; Gulam Manji, MD

## 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 will celebrate its fifth anniversary this year with several accomplishments. Over the last four and half years, the Institute continued to grow and now includes five core faculty, eleven associate faculty members, five affiliate faculty members, three research scientists, six postdoctoral research scientists, fourteen graduate students, nine interns and four staff members.

We were thrilled to welcome two new core faculty this year. Dr. Sanja Vickovic, and Dr. Bianca Dumitrascu is joining this January. The Institute invited Dr. David Tourigny to become an affiliate member. He was previously an associate research scientist at the IICD and recently became a Birmingham Fellow in the School of Mathematics at the University of Birmingham, UK.

The IICD and the Zuckerman Mind Brain Behavior Institute recently set up a new serial two-photon tomography (STPT) system. The project, spearheaded by IICD Associate Member Darcy Peterka, will allow the development of new approaches to image and interrogate the tumor microenvironment with single-cell resolution. The Institute continues to establish extensive collaborations with various departments and research centers. In particular, the IICD strengthened its partnership with the Herbert Irving Comprehensive Cancer Center through research collaborations with Dr. Peter D. Canoll (with Darcy Peterka for the STPT system) and Dr. Aaron D. Viny (with Russell Kunes) and supporting joint members.

# Precision Medicine Awards

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 University's commitment to supporting diverse, cross-disciplinary research targeting the promise of precision medicine. Each team will receive a one-year \$100,000 grant to support their research. The five projects are being led by principal investigators Ibrahim Batal, MD, associate professor of pathology and cell biology at Columbia University Vagelos College of Physicians and Surgeons (VP&S); Brent Stockwell, PhD, professor and chair of biological sciences at Columbia University; Marie-Pierre St-Onge, PhD, associate professor of nutritional medicine (in Medicine and the Institute of Human Nutrition) at VP&S; Raju Tomer, PhD, assistant professor of biological sciences at Columbia; and Kelley Yan, MD, PhD, assistant professor of medicine and of genetics and development at VP&S. Congratulations to the winning teams

## **The Immunopathology of Donor-Derived APOL1 Nephropathy**

**Lead Investigator: Ibrahim Batal, MD**

**Co-investigators: Kevin Gardner, MD, PhD, professor of pathology and cell biology; Barry Freedman, MD, professor of medicine and chief of nephrology at Wake Forest School of Medicine; Iuliana Ionita-Laza, PhD, professor of biostatistics**

Kidneys transplanted from Black donors have a shortened survival compared to white donors, which has been attributed to variants of the apolipoprotein L1 (APOL1) gene that is enriched in Black population. Black patients with kidney failure often receive kidneys from Black donors and therefore are more likely to receive kidneys with APOL1 variants that predispose them to early transplant failure. Donor-transmitted APOL1-transmitted kidney diseases are still poorly understood. The team will incorporate precision donor-screening technologies, innovative immunologic studies, and state-of-the-art digital microscopy techniques to better understand the mechanisms of donor-transmitted APOL1-associated kidney diseases, an area ripe for research. This project could improve distribution of donated kidneys in a subset of donors with APOL1 variants, facilitate discovery of more precise treatment, and expand overall understanding of the role of APOL1 in chronic kidney disease at large.

## **Optimization of Small Molecules that Restore Enzyme Activity to R152H GPX4**

**Lead Investigator: Brent Stockwell, PhD**

**Co-investigators: Farhad Forouhar, PhD, associate research scientist at the HICCC; Mohammed N. AlQuraishi, PhD, assistant professor of systems biology**

Dr. Stockwell and collaborators have in prior research identified a specific R152H single amino acid alteration in the lipid repair enzyme, called GPX4 that is associated with a severe phenotype involving developmental issues, including a rare progressive disorder called Sedaghatian-type Spondylometaphyseal Dysplasia (SSMD) for which there is no cure. In laboratory studies, the researchers uncovered small molecules that can activate the variant, and potentially reverse its developmental damage in patients. However, these novel compounds need to be optimized, in terms of their properties and potency, to allow for testing in animals and ultimately in human clinical trials. In this new project, the team will build on prior results, validate the novel compounds in an animal model of R152H GPX4, and ultimately serve as corrective drugs to reverse the effect of this variant in patients.

## **Study of Sleep as an Essential Factor in Aging: Analysis of Biological Biomarkers as Mediators in the Development of Cardiovascular Diseases**

**Lead Investigator: Marie-Pierre St-Onge, PhD**

**Co-investigators: Lawrence Honig, MD, PhD, professor of neurology; Rocio Barragan, PhD, postdoctoral research fellow at University of Valencia; Christian Dye, PhD, postdoctoral research fellow in Columbia's Department of Environmental Health Sciences; and Bin Cheng, PhD, professor of biostatistics**

Life expectancy has increased in recent decades, leading to an increase in chronic diseases of old age, like cancer, diabetes or heart disease. Aging also comes with a decrease in the heart's ability to contract properly, and research has shown a strong link between aging and the development of heart disease, which remains the leading cause of death worldwide.

Many factors change with age. Among those are changes in the genes that can be used as a "biological clock" to calculate life expectancy. This "biological clock" can be changed by two things the components of cells in the body that carry genetic information and the parts of the genes that are altered by the environment. Dr. St-Onge and team will focus on how our sleep patterns affect biological factors that drive cardiovascular disease. The team will investigate whether sleep reduction causes changes in genes, and how these genetic changes can influence heart health.

## **Towards Precision Psychiatry: An In Vitro Model of Schizophrenia-associated Network Pathophysiology**

**Lead Investigator: Raju Tomer, PhD**

**Co-investigators: Joseph Gogos, MD, PhD, professor of physiology and cellular biophysics, neuroscience and psychiatry (in the Zuckerman Mind Brain Behavior Institute); Sander Markx, MD, PhD, assistant professor of clinical psychiatry**

Brain disorders account for 13% of the global disease burden, yet few therapeutic options are available that reduce the disability and mortality associated with these diseases. This is partly due to the immense complexity of the human brain function, which has made it challenging to develop a comprehensive understanding of what drives brain disorders. The team is addressing some of these challenges by building upon the advances in the field of human brain organoids (mini-brains) to develop an in vitro model of patient-specific neural circuit functional deficiencies associated with brain disorders. Their project will focus on two key genetic variants that are the strongest genetic risk factors linked to schizophrenia. For both these genetic conditions, the researchers also have access to cell lines that were derived from human subjects who have previously been diagnosed with schizophrenia, and also have undergone multiple EEG recordings (a test that detects abnormalities in brain waves) for the assessment of seizures. This approach may open possibilities for in vitro modeling and systematic comparative characterization of network-level effects of different mutations linked to psychiatric and neurological disorders, beyond schizophrenia.

## **Central Memory T cells in the Human Colorectal Cancer Immune Microenvironment**

**Lead investigator: Kelley Yan, MD, PhD**

**Co-principal investigator: Arnold Han, MD, PhD, Robert F. Loeb Assistant Professor of Medicine and assistant professor of microbiology and immunology**

Although mouse models have proven invaluable in the study of human cancer, no mouse model can completely recapitulate human cancer. Recently, methods to culture and maintain human cancers in the lab have advanced our understanding of human cancer biology. However, because immune cells are present throughout the body and not necessarily localized to tumors, such culture methods have not been applied to the study of immune response to cancers. The team's preliminary data suggests that it is possible to recapitulate important components of the human immune system with human tumors, including a particularly important immune cell population with therapeutic potential, through in vitro culture. This project will investigate the feasibility of culturing and manipulating human tumor immunity in a self-contained and experimentally tractable culture platform. The aim is to establish the foundation for transformative future experiments with many precision medicine applications.

## **Precision Medicine Scholar's Day**

On November 30, 2022, the Vagelos College of Physicians & Surgeons Columbia Precision Medicine Initiative, Irving Institute for Clinical and Translational Research, and the Herbert Irving Cancer Research Center held our annual Precision Medicine Scholars' Day, an internal meeting featuring research presentations by the Pilot Award winners.

Speakers included:

Katrina Armstrong, MD

Xuebing Wu, PhD

Marie-Pierre St-Onge, PhD

Srilaxmi Bearely, MD, MHS

Brent Stockwell, PhD

Richard Carvajal, MD

Chi-Min Ho, PhD

Ibrahim Batal, MD

Keynote Speaker: Christine Kim Garcia, MD, PhD

Brian Henick, MD

Kelly Yan, MD

Tal Korem, PhD

Raju Tomer, PhD

Yufeng Shen, PhD

The event program with talk abstracts can be found [here](#).

# 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 was directed by a Steering Committee of faculty chaired by Paul Appelbaum, MD and Gil Eyal, PhD. In the 2022-23 academic year, Dr. Rebecca Jordan-Young replaced Dr. Eyal as co-chair of the Steering Committee.

## Precision Medicine: Ethics, Politics and Culture (PMEPC)

Sponsored by the PM&S program, PMEPC supports graduate fellowships and a series of scholarly events. During the 2021-22 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. Because of the Covid-19 pandemic, all events were held remotely.

Drs. Sabatello and Eyal continue to co-lead the series in 2022-23. The public lectures for this year will include Santiago J. Molina, PhD, on the practice and politics of genome editing; Mildred Cho, PhD, on artificial intelligence (AI), digital twins and virtual patients; Elaine O. Nsoesie, PhD, on big data and health equity; and Chris Donohue, PhD, on enhancement for disability and genome ethics. Details on the series, including the dates of the 2022-23 events, can be found [here](#).

In the 2021-22 program, the PMEPC sponsored five Graduate Fellows. All of the Fellows participated in our series of public talks and small group meetings. The 2021-22 Fellows were: Colby Lewis (Biostatistics); Chloe Cheung (Genetic Counseling); Sasinya Scott (Epidemiology); Merwa Naveed (Sociomedical Sciences); Jay Al-Hashimi (Bioethics)

As part of the Fellowship, one of the fellows, Chloe Cheung, completed her thesis on polygenic risk scores and behavioral genetics.

Five new Fellows have been selected for the 2022-23 PMEPC Graduate Fellowships. Each of new Graduate Fellows will develop a publishable research paper relating to PM&S and PMEPC faculty are working with them to refine the subjects of their projects.

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

Research conducted with PM&S funding resulted in a paper on the impacts of polygenic scores for educational attainment that is under review at *Genetics in Medicine*. Members of the Steering Committee also published articles addressing a variety of issues related to the ethical, legal and social impact of precision medicine, among them:

- Polygenic embryo screening;
- Data sharing and community engagement;
- Genome privacy and trust;
- Challenges for precision public health communication;
- Diversity and inclusion in precision medicine research;
- Moving away from continental ancestry in genomic research;
- Direct-to-consumer genetic relative-finder services;
- Genetic testing and precision education;
- Genetic attributions and perceptions of naturalness;

- Sharing of genetic results with family members;
- Addressing genetic variants of uncertain significance;
- Reducing inequity in variant interpretation based on ancestry;
- Potential solutions to health disparities in genomic medicine;
- Causal attribution and attitudes to genetic testing among people with schizophrenia;
- Practical considerations for reinterpretation of individual genetic variants.

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 2021-22 academic year, the Center hosted nine scholarly presentations. Presenters included:

- Daniel Navon, Ph.D., Department of Sociology, University of California, San Diego
- Shirley Sun, PhD, School of Social Sciences, Nanyang Technical University, Singapore
- Tim Yu, MD, PhD, Dept. of Pediatrics, Harvard Medical School
- Danton Char, MD, Dept. of Anesthesiology, Stanford University
- Shawneequa Callier, JD, MA, Dept. of Clinical Research and Leadership, George Washington Univ.
- Kathryn Phillips, PhD, Dept. of Clinical Pharmacy, University of California, San Francisco
- Ben Berkman, JD, MPH, Dept. of Bioethics, National Institutes of Health
- Susan Gelman, PhD, Dept. of Psychology, Univ. of Michigan
- Nathaniel Comfort, PhD, Dept. of the History of Medicine, Johns Hopkins University

Presentations planned for the 2022-23 academic year include:

- Naomi Wray, PhD, University of Queensland, Australia
- Anna Lewis, PhD, Harvard University
- Jordan Smoller, MD, ScD, Harvard University
- Kenneth Kendler, MD, Virginia Commonwealth University
- Steve Hyman, MD, Harvard University
- Anna Docherty, PhD, University of Utah
- Kyle Brothers, MD, PhD, University of Louisville
- Ingrid Holm, MD, MPH, Harvard University
- Paul S. Appelbaum, MD, Columbia University

All talks will take place online during 2022-23, Mondays, 12:00 - 1:00pm. To receive a link to each talk, interested individuals should send an email to [alfa.garcia@nyspi.columbia.edu](mailto:alfa.garcia@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, in May 2020 on Precision Medicine & Society: International Perspectives; and in May 2021 on Precision Medicine & Society: New Perspectives, we held our Fourth Annual Conference in May 2022, this time dedicated to the emerging field of exposomics. The field addresses how environmental factors, inclusive of social and economic disparities, interact with genomic, epigenetic and cellular processes in affecting health. The conference brought together natural scientists and social scientists who explore the impact of environmental exposures from their respective perspectives.

Some of the themes discussed were the ethical and methodological issues raised by exposomics research on the causes and mechanisms of environmental exposure, especially in vulnerable communities; gene x environment interactions and parsing genomic vs. environmental influences; and how social and physical factors interact in the causation and impact of environmental exposures. The program can be viewed online [here](#), with recordings of each panel from the 2022 conference [here](#). The names and biographies of the speakers can be accessed here. Planning for the 2023 conference, which will focus on race and racialization in/and precision medicine, is currently under way.

## PM&S Seed Grants

The announcement for seed grant funding for the 2022-23 academic year can be found [here](#). We had a very successful Scholars' Day featuring the seed grant recipients from the previous two rounds of funding who presented their work to the Columbia community. The event program for this can be found [here](#).

# Educational Initiatives

## Precision Medicine: Biological, Social and Ethical Implications

Following on the successful course, Economics of Precision Medicine, offered in Spring 2020 by Bhaven Sampat in the Department of Health Policy and Management at the Mailman School of Public Health, the PM&S Program supported the first undergraduate course at the University on precision medicine entitled Precision Medicine: Biological, Social and Ethical Implications. The course was taught by members of the faculty in Biochemistry (Samuel Sternberg), Sociology (Gil Eyal) and English (Rachel Adams). The course covered the scientific foundations of precision medicine, its social dimensions, and the fundamental humanistic questions and challenges raised by this discipline. Believing in the importance of educating undergraduate students in the concepts involved in precision medicine, the course was structured as an introduction to precision medicine, particularly for the non-scientist student, but also explored issues relevant to students planning a career in science and medicine.

