CLEMSON UNIVERSITY
CENTER FOR HUMAN GENETICS

The Transcript

Newsletter of the Center for Human Genetics at Clemson University **Spring, 2025**

From the Director

As we enter a new academic semester, I am relieved that everyone at the Center for Human Genetics survived hurricane Helene without extensive damage other than the inconvenience of being without power for several days. I want to thank those of you who managed to get to the building and make sure fly stocks, cell cultures and our HPC were kept safe.

Fortunately, December graduation could proceed as planned. Congratulations to Spencer Hatfield for successfully defending his dissertation and being awarded the doctoral degree in genetics. Spencer will stay with the Mackay and Anholt laboratory for a while as a postdoctoral fellow to develop Drosophila models for substance use disorders with support from a grant from the National Institute on Drug Abuse. Congratulations also to Rebecca Bishop and Madeline Santana for completing their Master of Science degrees. Armed with a strong foundation in human genetics, Madeline returns to the Dominican Republic to continue her work as a physician treating pediatric patients.

Dr. Trudy F. C. Mackay, FRS, is the Self Family Endowed Chair of Human Genetics. She is a Fellow of the Royal Society of London, a member of the National Academy of Sciences and the National Academy of Medicine of the USA, a member of the American Philosophical Society, and recipient of the 2016 Wolf Prize.

Since its inception in July 2018, the Center for Human Genetics has undergone enormous growth. We currently are 30 affiliated faculty strong with 8 postdoctoral fellows, 32 students and 14 staff members. Despite the geographic diversity between Self Regional Hall in Greenwood, the Clemson University campus and affiliated members at the Greenwood Genetic Center, we have been able to sustain a social and academically cohesive human genetics community. This success can be credited to the active participation of our faculty, postdocs, students and staff members in our academic activities, including our weekly Advances in Human Genetics meetings, our monthly Distinguished Lectures in Human Genetics series, our monthly lunch-and-learn sessions and annual events that have become traditions, including the Darwin lecture, the summer symposium and the Fall retreat of the Center of Biomedical Research Excellence in Human Genetics.

The spring semester of 2025 is full of academic excitement. Our Distinguished Lectures in Human Genetics series will feature five outstanding speakers: Dr. Jef Boeke, Director of the Institute for Systems Genetics at New York University; Dr. Rodolphe Barrangou, Todd R. Klaenhammer Distinguished Professor in Probiotics Research in the Department of Food, Bioprocessing and Nutrition Sciences at North Carolina State University; Dr. Nancy Cox, Mary Phillips Edmonds Gray Professor of Genetics and Director of the Vanderbilt Genetics Institute; Dr. Diana Bianchi, Director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development; and Dr. Nancy Bonini, Florence R.C. Murray Professor of Biology at the University of Pennsylvania.

The 2025 Darwin lecture will feature Dr. Michael Purugganan, Silver Professor of Biology at New York University, who will describe domestication and the evolution of crops. This year Darwin's lecture will foreshadow the theme of our summer symposium: "Evolutionary Genetics of Human Health and Disease."

I am pleased to report that the Phase1 proof-of-concept stage of the Clemson University Precision Medicine project has been successfully completed with an enrollment of 200 ethnically diverse individuals reflecting the demographic composition of the state of South Carolina. We have collected and analyzed de-identified genomic information with de-identified electronic health records and survey information about lifestyles and health histories. Our goal is to move on to Phase 2, which will expand this project to 10,000 individuals. Our ultimate goal is to enroll 100,000 or more individuals across South Carolina to establish a database for predictive medicine.

The Center for Human Genetics remains committed to a broad vision that encompasses all aspects of human genetics, while focusing especially on areas at the scientific frontier, elucidating the regulatory functions of non-coding elements of the genome and explore gene regulatory networks and developing computational and statistical tools to advance accuracy of disease risk prediction and precision medicine.

We will continue to provide a state-of-the-art genomics and bioinformatics infrastructure to support our ambitious vision and an academic environment that promotes creativity and innovation. I have enormous confidence in the dedication of our faculty, the motivation of our students and postdocs and the expertise of our staff.

As we continue our journey together, I wish each of you a great Spring semester! Go Tigers!

Celebrating Dr. Spencer Hatfield's Achievements

by Alp Ummet

On October 22, 2024, Spencer Hatfield successfully defended his Ph.D. dissertation, titled *"Drosophila Model of Cocaine Use Disorder,"* earning his doctoral degree in Genetics under the mentorship of Drs. Trudy Mackay and Robert Anholt.

Spencer graduated as an Honors Carolina Laureate from the University of North Carolina at Chapel Hill in 2019, earning a B.S. in Biology with a minor in Chemistry. Shortly thereafter, he began his Ph.D. studies in Genetics at the Clemson University Center for Human Genetics, where he focused on modeling cocaine use disorder (CUD) in *Drosophila melanogaster*.

Cocaine use disorder is a major socioeconomic problem, with approximately 20% of cocaine users developing addiction. Genetic background plays a significant role in susceptibility to CUD. To explore genetic variation in susceptibility to cocaine, Spencer's dissertation utilized fruit fly models with diverse genetic backgrounds to uncover the genetic underpinnings of cocaine consumption and preference.

Toward this goal, Spencer conducted a large-scale behavioral screen using the *Drosophila* Genetic Reference Panel (DGRP), a collection of inbred wild derived fly lines with fully sequenced genomes. Together with Joshua Walters and Brandon Baker, Spencer developed the Microplate Feeder Assay (MFA), a high-throughput device enabling precise quantification of cocaine consumption across 600 DGRP lines. By exposing flies to cocaine and control solutions for 22 hours, he assessed cocaine preference for each DGRP line. The results showed significant sexual dimorphism and a subsequent genome-wide association study (GWAS) identified numerous candidate genes with human orthologs, many of which had not been previously linked to CUD, underscoring the translational potential of his work.

In addition to behavioral studies, Spencer investigated the cell-specific transcriptomic responses to cocaine in *Drosophila* brains, revealing sexually dimorphic gene networks by allowing flies to consume a fixed amount of cocaine and then dissecting their brains for single-cell RNA sequencing. These findings highlighted previously overlooked cell types with significant roles in cocaine response. By integrating behavioral data with transcriptomic insights, Spencer demonstrated the utility of *Drosophila* in cross-species preclinical drug discovery. Notably, he showed that ibrutinib - a drug used to treat chronic lymphocytic leukemia - alleviated cocaine-induced seizures in Drosophila, suggesting that repurposing of ibrutinib can be useful for treating certain aspects of CUD.

Jeffrey 'Spencer' Hatfield

During his studies, Spencer received a Ruth L. Kirschtein Predoctoral Individual National Research Service Award and had the opportunity to present his work at various conferences, including at the National Institute on Drug Abuse Genetics and Epigenetics Cross-Cutting Research meeting as well as the International Behavioral and Neural Genetics Society's Genes, Brain and Behavior meetings.

Spencer's innovative contributions have established a solid foundation for the use of *Drosophila* in CUD research. He continues his research on the genetics of substance use disorders as a postdoctoral fellow at the Clemson University Center for Human Genetics.

Congratulations, Spencer!

Alp Ummet is a graduate student in the Department of Genetics and Biochemistry and the Center for Human Genetics at Clemson University.

The 2024 Center of Biomedical Research Excellence in Human Genetics Retreat

by Monireh Pana and Xiao Li

The 2024 COBRE Retreat in Human Genetics, held on October 25 at the Greenwood Genetic Center, convened the COBRE leadership team, advisory committees, and project and pilot leaders. This retreat served as a platform for presenting cutting-edge research, fostering collaborative efforts, and receiving expert feedback, with attendees contributing to insightful discussions.

The symposium opened with a warm welcome and brief introduction by Dr. Trudy Mackay, who then invited the research project leaders to present their work, setting the stage for an engaging session of scientific discussions.

Miriam Konkel presents her work

Andrei Alexandrov discussed his lab's efforts to uncover regulatory pathways involved in the biogenesis of long non-coding RNAs using human cell models. His lab's development of ultra-high throughput technology led to the discovery of two novel components that regulate over 95% of total RNA in human cells, providing new potential targets for anti-cancer therapies.

Miriam Konkel presented her research on telomere-to-telomere (T2T) sequencing, which enables fully haplotype-resolved genome assemblies. She investigates mobile element families to track evolutionary patterns and identify structural variants that influence gene expression, underscoring the potential of T2T sequencing to advance precision medicine and improve understanding of genetic diversity.

Aaron Masino presented an innovative method for improving rare disease diagnostics using natural language processing (NLP) models to identify genotype-to-phenotype associations. His approach demonstrated promising results in tests across 5,000 simulated diseases, offering the potential to streamline the diagnostic process for rare diseases, even in noisy data.

Gavin Arno discussed the application of Oxford Nanopore sequencing to diagnose Inherited Retinal Dystrophy (IRD), highlighting its effectiveness in identifying pathogenic variants in *RPGR* and *ABCA4*, which are frequently overlooked by traditional sequencing methods. This technology could significantly improve diagnostics for rare diseases.

The symposium included presentations from COBRE Pilot Project leaders. Christopher Farrell presented his research on multidrug resistance in the treatment of colorectal cancers. Colorectal cancer causes 50,000 deaths annually in the U.S., with multidrug resistance (MDR) playing a significant role. Dr. Farrell's work focuses on how statins, typically used for cardiovascular conditions, may increase P-glycoprotein (Pgp) levels, contributing to MDR in chemotherapy-naïve colorectal cancer cells. Using samples from 35 colorectal patients, his research aims to identify biomarkers that could predict chemotherapy resistance in statin-treated patients.

Shyamalika Gopalan's research addresses the challenges of developing robust epigenetic age prediction tools that account for population structure, genetic background, and environmental factors. By analyzing DNA methylation in individuals from two admixed populations, she highlighted the need to develop tools to minimize interpopulation biases and improve the accuracy of age prediction, with implications for both forensic investigations and understanding biological variability in aging.

Subham Dasgupta presented his research on the effects of the flame retardant TBBPA on zebrafish embryonic development. His study revealed that TBBPA exposure during gastrulation causes transcriptional changes in over 200 genes. Notably, he found increased histone H3 acetylation in exposed embryos, suggesting that TBBPA disrupts chromatin assembly through histone modification. This research provides a foundation for future studies on the developmental toxicities of flame retardants.

Qing Liu investigates the role of the transcription factor GATA4 in regulating mitochondrial function during heart development. Using CRISPR-edited stem cell models, he demonstrated that GATA4 is essential for the expression of mitochondrial genes and proper cellular metabolism. His findings contribute to understanding the gene-regulatory mechanisms underlying mitochondrial dysfunction in cardiovascular diseases.

Kelsey Witt Dillon proposed a computational framework to study gene flow and its effects on genetic diversity in isolated populations. By analyzing both ancient and modern admixed genomes, she aims to identify the long-term effects of admixture on human health, adaptation, and the evolution of complex traits, with potential applications in understanding morbidity and mortality patterns across diverse populations.

The 2024 COBRE Retreat highlighted groundbreaking research in human genetics and fostered valuable collaborations. We eagerly anticipate the continued progress of these projects and their contributions to the 2025 COBRE Project Leaders Symposium.

Monireh Pana and Xiao Li are doctoral students in the Departments of Genetics and Biochemistry and Biological Sciences, respectively, and in the Center for Human Genetics at Clemson University.

Human Evolutionary Adaptation – as Revealed by Our Genomes

by Ashley Kirby

On Friday, September 13th, the Clemson University Center for Human Genetics hosted Dr. Rasmus Nielsen. Nielsen is a professor of computational biology at the University of California Berkeley and a professor of biology at the University of Copenhagen. He was elected to both the National Academy of Sciences and the Royal Danish Academy of Sciences.

Nielsen's work centers on the intersection of genetics and evolutionary adaptation. He has leveraged computational power and the availability of large-scale genomic data to perform statistical and population genetics analyses, advancing our understanding of natural selection, population variation, and demography. Several of Nielsen's computational methods are widely used, including methods to identify positive selection, infer demographic histories, detect selective sweeps, and analyze Next Generation Sequencing (NGS) data.

Nielsen's presentation, "Human evolutionary adaptation – as revealed by our genomes", highlighted his work in statistics and population genetics, particularly the use of coalescent trees, which trace shared ancestry of sampled individuals backward in time to a common ancestor, to untangle evolutionary relationships. When this approach is applied to genomic data, millions of coalescent trees result due to recombination. The joint collection of coalescent trees and the ways in which they are connected is called an ancestral recombination graph (ARG). Nielsen and colleagues developed SINGER (Sampling and INferring of GEnealogies with Recombination), a robust and scalable computational tool that leverages ARGs to make inferences about natural selection, including estimation of selection coefficients and mutation trajectory. To demonstrate that ARGs allow use of modern population genomic data to approximate the likelihood of selection acting on a locus and allele frequencies of variants in the past, Nielsen discussed lactase persistence in Europeans. Individuals with continuous expression of lactase can consume milk, while those with reduced expression exhibit lactase non-persistence and are unable to digest milk into adulthood. Nielsen and colleagues analyzed the causal variant in the *MCM6* gene in individuals with and without lactase persistence. Those carrying the causal variant exhibited reduced variation and recent coalescence at the *MCM6* locus, indicating strong positive selection on the variant associated with lactase persistence, likely as an adaptation to dairy farming introduced by pastoralist populations.

To further demonstrate selection on genomic variants, Nielsen shared his previous work on Tibetan altitude adaptation. The Tibetan plateau is located at an altitude of 4 km, where the partial pressure of oxygen is only 60% that of sea level. Under these conditions, humans exhibit a plastic response, augmenting production of red blood cells (RBC). However, this increases blood viscosity, heightening the risk of cardiovascular disease, stroke, and pregnancy complications. Remarkably, Tibetan individuals are adapted to high altitude conditions and maintain lower RBC counts. A scan for regions of selection uncovered two causative

Dr. Rasmus Nielsen

variants in the hypoxia response pathway, *EPAS1* and *EGLN1*, with evidence of strong positive selection in the Tibetan population. Nielsen and colleagues compared haplotypes of Tibetans to the closely related lowland Han Chinese population and found that they deviated more than expected. Further, the Tibetan haplotype was not shared with any of the 1,000 Genomes populations. Ultimately, it was matched to DNA from a Denisovan, a now-extinct group of archaic hominins, providing evidence of interbreeding between ancient hominins and the ancestors of modern Tibetans. This is an example of adaptive introgression, when interbreeding between two groups results in acquisition of variants that confer a fitness advantage and subsequently undergo strong positive selection. Stories like this show how modern humans successfully adapted to diverse environments around the world. According to Nielsen, it was likely a combination of technological advancement and the acquisition of adaptive traits from archaic hominins already adapted to the environmental conditions.

Nielsen's work has furthered our understanding of human evolution, connecting the dots between our evolutionary past and features associated with modern humans. One of his goals is to translate evolutionary understanding into a medical context. For example, recent work in his lab revealed that elevated risk of multiple sclerosis (MS) in Europeans emerged from migrations of ancient steppe pastoralist populations into Europe approximately 5,000 years ago. In summary, Nielsen's talk conveyed that the complexities of modern human genetic variation are inextricably linked to the events and adaptations of our past, and that understanding our evolutionary history from both a scientific and cultural perspective is critical to resolving modern-day questions.

Ashley Kirby is a graduate student in the Department of Genetics and Biochemistry and the Center for Human Genetics at Clemson University.

Insights into the Biology of Human Traits from GWAS and Functional Genomics

by Khushi Goda

The Clemson University Center for Human Genetics hosted Dr. Jonathan Pritchard on October 28, 2024 as part of its Distinguished Lectures in Human Genetics series. Dr. Jonathan Pritchard is a distinguished geneticist at Stanford University who specializes in human genetic variation and evolution. He is known for his groundbreaking development of the STRUCTURE algorithm, a widely used tool for determining population structure and estimating individual admixture. This algorithm has been instrumental in various fields, including conservation biology and ecology, and underlies ancestry reports used by companies like 23andMe and Ancestry.com. Pritchard's laboratory employs state-of-the-art statistical and computational methods, such as the STRUCTURE algorithm for population genetics, GWAS tools for linking genetic variants to traits, and CRISPR-based methods like Perturb-Seq for exploring gene regulatory networks, to address questions in genomics and evolutionary biology.

Over the course of his career, Pritchard has significantly advanced our understanding of how genetic variation influences human traits and evolution with groundbreaking contributions to the fields of population genetics and genomics. His work has earned him prestigious awards, including the Mitchell Prize from the American Statistical Association and the International Society of Bayesian Analysis and the Edward Novitski Prize from the Genetics Society of America.

Pritchard presented a seminar titled “How GWAS and functional genomics provide insight into molecular pathways of human trait biology." He started by providing background on genome-wide association studies (GWAS) and their role in linking genetic variants to traits. Highlighting both the strengths and challenges of modern GWAS, he explained its power in identifying significant genome-wide signals and discussed challenges such as the gene linking problem and the difficulty in estimating gene effects.

To better quantify the relationship between gene expression and phenotype, Pritchard introduced Gene Dose Response Curves (GDRCs). This method addresses challenges in interpreting nonlinear gene dosage effects by incorporating real-world, non-monotonic data patterns. Loss of function (LoF) mutations and duplications serve as key data points, providing insights into gene effects. Studies on traits like LDL cholesterol and hemoglobin exemplify how LoF mutations clarify causal pathways.

Pritchard also introduced Perturb-Seq, a CRISPR-based method that systematically knocks down genes to study their regulatory effects. He discussed using Perturb-Seq data to understand genetic associations and gene regulatory networks in the K562 cell line. He also addressed the challenges of using K562 as a model for human traits and emphasized the importance of integrating Perturb-Seq data with GWAS and burden tests. Key findings included significant enrichment of GWAS signals in K562 active chromatin for traits like mean corpuscular hemoglobin, red blood cells, and immature reticulocytes. He also highlighted

Dr. Jonathan Pritchard

using machine learning methods such as gene base to de-noise burden signals and applying collaborative non-negative matrix factorization for dimension reduction. The discussion also touched on the complexities of regulatory networks and the potential for future studies to enhance our understanding of gene regulatory networks and their relevance to human biology.

Despite its power, interpreting GWAS remains challenging due to factors such as gene-environment interactions, data complexity, and difficulties in linking genetic variants to specific biological pathways. Pritchard emphasizes that the core challenge going forward is to figure out how to put together association studies with modern functional genomics tools to build genome-scale interpretive models, which his laboratory will continue to explore.

The seminar ended with a highly interactive Q&A session which focused on using UK Biobank data for complex traits, the impact of single-cell technology on gene regulatory networks, and the challenges of modeling complex traits. Specific projects mentioned included studying the regulation of micro exons, alternative splicing, and gene-by-environment interactions. The conversation also touched on the limitations of current technologies, the importance of machine learning in analysis, and the potential for future research directions, such as expanding large-scale Perturb-Seq data to better connect genetic associations to biological pathways or refining gene regulatory network models for better prediction and mechanistic understanding of traits and diseases.

Pritchard's pioneering work inspires and shapes the future of human genetics, providing a roadmap for integrating cutting-edge genomics tools to unravel the complexities of human biology and disease. His dedication to addressing fundamental questions in genetics ensures that his research will have a lasting impact on the field, driving progress in personalized medicine and beyond.

Khushi Goda is a postdoctoral fellow in the Department of Genetics and Biochemistry and the Center for Human Genetics at Clemson University.

A Conversation with Shahid Mukhtar

Could you briefly describe your research interest in human genetics?

My research interests center on non-canonical genetic elements, an often-understudied area in eukaryotic systems. Leveraging systems biology approaches, we explore their roles across complex biological networks. Specifically, in human systems, my team focuses on two main areas. We investigate the role of non-canonical genetic elements, such as orphan genes and extrachromosomal circular DNA (eccDNA), in Alzheimer's Disease (AD) and brain strokes. In AD, which impacts over 50 million people worldwide, we focus on how these elements contribute to protein misfolding, neuroinflammation, and cellular stress that destabilize brain homeostasis, aiming to identify novel therapeutic targets. Additionally, we explore how environmental pollutants like macro- and nanoplastics interact with these genetic elements to influence brain health, providing insights into their role in disease onset and progression.

What do you see as the most important unanswered question in genetics?

A key unanswered question in genetics is how gene-environment interactions shape phenotypic outcomes, especially in multifactorial diseases. While genetic mapping has advanced, our understanding of the dynamic interplay between genetic variations and environmental factors remains limited. Additionally, the role of epigenetics in transmitting heritable changes in gene expression without altering DNA sequences is crucial to understanding health and disease. Another challenge lies in integrating multi-omics data to develop predictive models of genetic functions, which could transform personalized medicine.

What is the most rewarding part of your research?

The most rewarding aspect of my research is deepening our understanding of biological systems while mentoring the next generation of scientists. Seeing students and postdocs develop into independent thinkers who make meaningful scientific contributions is fulfilling. Additionally, witnessing the translational impact of our discoveries reinforces why I chose this career - creating knowledge that benefits humanity and the environment.

Coming from Alabama, what attracted you to join the faculty at Clemson University?

Clemson University's commitment to research excellence, particularly in personalized medicine through initiatives led by Drs. Trudy Mackay and Robert Anholt, was a major draw for me. Additionally, the chance to contribute to state-of-the-art agricultural genomics initiatives resonates with my long-term objectives. Clemson offers incredible opportunities for collaboration and resources that support ambitious scientific goals.

The university's strategic plan, *Clemson Elevate*, aligns with my vision of advancing cutting-edge research while fostering inclusivity and student success. Beyond academics, Clemson's community-oriented culture and proximity to natural beauty, which appeals to my love for the outdoors, made the transition from Alabama both professionally and personally rewarding.

What advice can you give to young scientists who are at the beginning of their academic careers?

To young scientists, I advise embracing curiosity, persistence, and adaptability. Science is full of challenges, and resilience is essential. Foster lifelong learning, adopt interdisciplinary approaches, and collaborate with inspiring mentors and peers. Additionally, developing strong communication skills is crucial for advancing your career and ensuring your work has a broader societal impact.

What activities do you enjoy when you are not working in the lab?

When I'm not in the lab, I love spending time outdoors - whether it's hiking in nature, running with my older daughter, or simply soaking in the fresh air and serenity. I also enjoy playing pickleball with my daughters, which has become a fun and active way for us to bond. Recently, I've started a new hobby with my younger daughter - playing Wordle together as a team. Above all, spending quality time with my life partner and daughters is a source of immense joy and fulfillment.

Viewpoint: Predicting with Precision

by Robert Anholt

The last 100 years have seen enormous advances in medicine, including the development of drugs from aspirin to insulin that are universally effective in treating common ailments. Over time, awareness emerged that different individuals respond differently to, for example, pain medications with some requiring higher doses than others to be effective. And, of course, higher dosages are more likely to cause side effects.

With the advent of genomics at the turn of the century and increasingly cost-effective whole genome sequencing 'personalized' medicine has become all the rage. But has medicine in the modern era not always been personalized? Every surgical procedure is tailored to the individual and the personal relationship between the physician and the patient has long been one of the most highly valued attributes of the medical profession.

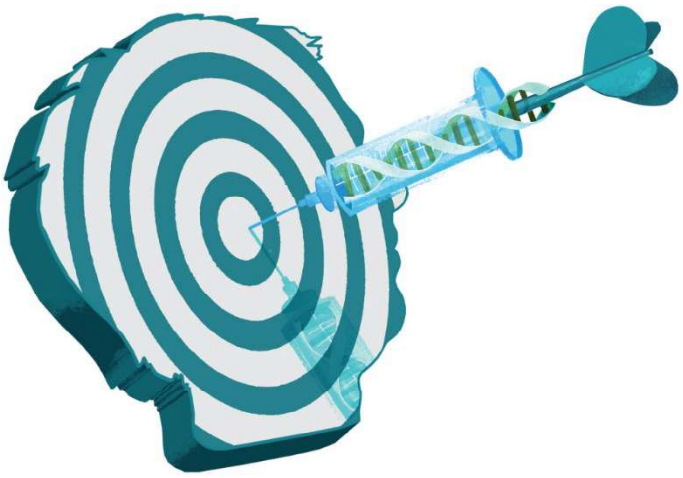
So, let's change the terminology: from 'personalized' medicine to 'precision' medicine. Perhaps, this change is only a matter of nuance which implies that treatments can be more effective (*i.e.*, precise) when individual disease-related genetic information is available. But precision medicine is, in principle, nothing new. Consider for example optometry or cataract surgery, where vision is corrected with extreme precision, or knee or hip replacement surgery, not to mention prostheses, which are exquisitely tailored to the individual patient with great precision.

So, what do we really mean when we talk about 'precision' medicine? The term implies assessment of disease risk by placing the genetic make-up of an individual in the context of available genetic information and - although still a challenge - lifestyle information and their interactions based on analyses of large databases, such as the UK BioBank or the All of Us project. I would argue that the term 'predictive' medicine is a more accurate description of this evolution of future medical practice than 'precision' medicine.

Are the terms 'personalized medicine', 'precision medicine' and 'predictive medicine' merely irrelevant semantic synonyms? No. The term 'predictive medicine' has different implications. Using the term 'prediction' immediately raises questions that illustrate the complexity of so-called precision medicine. For example, how accurate can predictions be if they are based only on genetic information?

There are few instances in which the manifestation of diseases can be predicted with 100% or near 100% accuracy and these are generally well defined monogenic Mendelian diseases. One example is the risk of developing Huntington's disease based on the number of glutamine repeats in the huntingtin protein. However, the heritability of disease risk, *i.e.*, the fraction of phenotypic variance that is due to genetic factors, is generally less than unity for common disorders, which places a limitation on the accuracy of risk prediction based merely on genetic factors.

Although numerous genome-wide association studies for complex diseases have been performed, risk prediction based on polygenic risk scores, that sum the risks associated with individual potentially pathogenic variants, remains



generally poor. This is due to several limitations. Non-additive effects that arise from gene-gene interactions are generally not considered in computing polygenic risk scores, but they may dramatically affect disease risk prediction. Detecting such interactions, especially higher order gene-gene interactions, is hampered by statistical limitations.

Another major challenge is incorporating environmental effects in risk prediction algorithms. Whereas genetic variants can be readily identified and classified, environmental conditions and developmental histories are heterogeneous and not readily quantifiable. In some cases, however, the role of specific lifestyles on disease risk are well defined. For example, individuals with genetic variants that may predispose them to lung cancer may never develop the disease unless they smoke. In most cases, however, it is challenging to predict how multiple aspects of lifestyles or environmental exposures can modulate disease risk. It is difficult to predict the risk for cardiovascular disease of a person who has a high fat diet but also exercises regularly. Environmental pollutants in industry-intensive locations can also profoundly affect disease risk dependent on individuals' genetic contexts. The interplay between detrimental and beneficial aspects of lifestyle or environmental exposure with genetic information poses the most significant challenge for predictive medicine.

Despite these challenges, however, major advances have been made, for example, designing optimal drug treatments for different types of breast cancer. However, these treatments are not predictive, but rather 'postdictive' as the disease manifestation has already occurred. They are, however, examples of true 'precision' medicine. It seems then that in summary, 'predictive' medicine and 'precision' medicine are two sides of the same coin. The challenge is forming the bridge between them.

Robert Anholt is the Provost Distinguished Professor of Genetics and Biochemistry and Director of Faculty Excellence in the College of Science at Clemson University. The opinions expressed in this article are his own.

Grants

Alexis Stamatikos received a five-year $1,906,250 grant from the National Heart, Lung, and Blood Institute to identify novel atheroprotective mechanisms.

Seminars

On Friday, **January 10**, at 2:30 pm, **Dr. Jef Boeke**, Director of the Institute for Systems Genetics at New York University, will present a seminar titled “Scaling up genome engineering in yeast and mammals.” The seminar will be held at 174 Poole Agricultural Center.

On Friday, **January 24**, at 2:30 pm, **Dr. Rodolphe Barrangou**, Todd R. Klaenhammer Distinguished Professor in Probiotics Research in the Department of Food, Bioprocessing and Nutrition Sciences at North Carolina State University, will present a seminar titled “Applications and implications of genome editing technologies.” The seminar is also part of the Provost’s Distinguished Lecture series and will be held at 174 Poole Agricultural Center.

On Wednesday, **February 12**, at 2:00 pm, **Dr. Michael Purugganan**, Silver Professor of Biology at New York University, will deliver the annual Darwin lecture titled “Domestication and the evolution of crops" The seminar will be held in BRC100.

On Monday, **March 3**, at 2:00 pm, **Dr. Nancy Cox**, Mary Phillips Edmonds Gray Professor of Genetics and Director of the Vanderbilt Genetics Institute, will present a seminar titled “Learning the biology of genes a few at a time — easier and more powerful than one at a time!” The seminar will be via Zoom, https://clemson.zoom.us/j/97768796700

On Monday, **March 31**, at 2:00 pm, **Dr. Diana Bianchi**, Director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development at the National Institutes of Health, will present a seminar titled “Non-reportable prenatal cell-free DNA sequencing results: what is the risk of maternal cancer?” The seminar will be via Zoom, https://clemson.zoom.us/j/97367778728.

On Monday, **April 7**, at 2:00 pm, **Dr. Nancy Bonini**, Florence R.C. Murray Professor of Biology at the University of Pennsylvania, will present a seminar titled “Insights into the brain from Drosophila models of human degenerative disease.” The seminar will be via Zoom, https://clemson.zoom.us/j/93624247158.

On Friday, **May 16**, from 9:00-5:00 pm, the Center for Human Genetics will host its annual **Summer Symposium on “Evolutionary Genetics of Human Health and Disease”** at the Arts Center of Greenwood, 120 Main Street in Greenwood. Speakers include Drs. Megan Dennis (UC Davis), John Lindo (Emory University), Scott Williams (Case Western University) and Antonio Capra (UC San Francisco). Breakfast and lunch will be provided.

Publications

(affiliates of the Center for Human Genetics are in bold font)

Badenetti L, Yu SH, Colonna MB, Hull R, Bethard JR, Ball L, **Flanagan-Steet H** and **Steet R**. 2024. Multi-omic analysis of a mucolipidosis II neuronal cell model uncovers involvement of pathways related to neurodegeneration and drug metabolism. *Mol Genet Metab* **143:**108596.

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Out and About

Robert Anholt has been appointed guest professor for the Master in Genetics Program at the Institute of Biomedical Sciences, Department of Neuroscience, Faculty of Medicine, University of Chile, Santiago, Chile, to deliver annual workshops on presentation skills. He also serves on the Intellectual & Real Property Committee of the Greenwood Genetic Center and the planning committee for the 2025 NIDA Animal Genetics Consortium meeting.

Ashley Kirby and **Gianni Martino** attended the Southeastern Population Ecology and Evolutionary Genetics meeting in October, which was hosted at Clemson University. Ashley presented a poster, and Gianni gave an oral presentation.

Miriam Konkel gave an oral presentation at the Cold Spring Harbor Transposable Element meeting. She also serves as guest editor for Genome Biology for the collection on transposable elements in genome evolution.

Xinyi Li presented a Biophysics Seminar in the Department of Physics and Astronomy at Clemson University on “Nonparametric regression for 3D point cloud learning. She presented invited talks at the 2024 Conference on Neural Information Processing Systems (NeurIPS 2024) in Vancouver, BC, Canada, the 2024 Joint Statistical Meetings in Portland, OR, and the 7th International Conference on Econometrics and Statistics (EcoSta 2024) in Beijing, China, where she organized and chaired sessions on “Advancement in Statistical Genetics and Genomics Study” and “Frontiers in Nonparametric Statistics and Functional Data Analysis.” She also attended the 2024 Hangzhou International Conference on Frontiers of Data Science in Hangzhou, China, and the 6th Pacific Causal Inference Conference (PCIC 2024), in Shanghai, China. She also organized an invited session at the 2025 Joint Statistical Meetings in Nashville, Tennessee, on “Innovations in Nonparametric and Functional Data Methods: Tackling Complex Data Challenges.”

Mark Loftus was an invited speaker at the American Society of Immunogenetics and Histocompatibility.

Trudy Mackay and **Robert Anholt** attended the 2024 Fall meeting of the American Philosophical Society in Philadelphia, PA.

Trudy Mackay was elected a Laureate Distinguished Fellow of the International Engineering and Technology Institute. She was also elected Member of the National Academy of Medicine.

Aaron Masino gave an invited presentation on artificial intelligence for phenotype discovery and recognition in support of rare disease research and diagnosis at the South Carolina Genetic, Counseling Society, 2024 Annual Education Meeting in Columbia, SC.

Aaron Masino and **Ranga Baminiwatte** presented a poster on artificial intelligence for unsupervised population phenotyping to uplift disease genotype to phenotype association discovery at the American Society for Human Genetics 2024 Annual Meeting in Denver, CO. They also gave a presentation on automated shared phenotype discovery in undiagnosed cohorts for rare disease research at the International Conference of Machine Learning Applications in Miami, FL.

Bibhu Simkhada attended the American Society for Human Genetics conference in Denver, CO, and represented the Center for Human Genetics and the College of Science at the 2025 Annual Biomedical Research Conference for Minoritized Scientists (ABRCMS) meeting in Pittsburgh, PA.

Allen Wu received a travel award to attend the 2024 Annual Meeting of the Society for Glycobiology at the Omni Amelia Island Resort in Amelia Island, FL.

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