ASHG 2021 Invited Sessions (as of June 2021)

Tuesday, October 19
3:30 – 5:00 pm ET

Genomic and epigenomic discoveries from the first truly complete assembly of a human genome
Moderators: Glennis Logsdon, PhD, University of Washington; Karen Miga, PhD, UCSC Genomics Institute

Since the initial release of the human genome sequence 20 years ago, human chromosomes have remained unfinished due to large regions of highly identical repeats clustered within centromeres, regions of segmental duplication, and the acrocentric short arms of chromosomes. However, recent advances in long-read sequencing technologies and associated algorithms have now made it possible to systematically assemble these regions from native DNA for the first time. In this session, we will present the first complete sequence of a human genome and provide an in-depth look at the newly resolved regions, their variation across individuals, and the resulting impact on human health, disease, and evolution. Our first speaker is a co-lead of the Telomere-to-Telomere (T2T) Consortium (https://sites.google.com/ucsc.edu/t2tworkinggroup), and he will introduce the session by unveiling the complete human genome and explaining the efforts to sequence, assemble, and validate the genome assembly. Our second speaker will present the genetic and epigenetic maps of all human centromeric regions and discuss their evolution across the hominid phylogeny over the last 25 million years. Our third speaker will focus on the segmental duplications found within the genome and discuss their transcriptional and epigenetic status. Finally, our fourth speaker will present the human methylome, with a particular focus on the epigenetic profile of newly resolved regions. At the end of the session, we will host a panel discussion to allow for a Q&A between the audience and each of our four speakers.

Speakers:
The complete sequence of a human genome. Adam Phillippy, PhD, NIH/NHGRI
Genetic, epigenetic, and evolutionary maps of endogenous human centromeres. Nicolas Altemose, PhD, UC Berkeley
Segmental duplications and their variation in a complete human genome. Mitchell Vollger, BS/BA, University of Washington
Long reads reveal epigenetic patterns in a complete human genome. Ariel Gershman, BS, Johns Hopkins University

Learning Objectives:
1. Explain why centromeres, segmental duplications, and other repeat-rich regions of the human genome have been historically challenging to resolve.
2. Identify recent advances in long-read DNA sequencing technology and assembly algorithms that are now allowing scientists to accurately assemble complex regions of the genome.
3. Describe genetic and epigenetic features of newly resolved regions of the human genome.
4. List remaining challenges to achieve telomere-to-telomere chromosome assemblies in diploid human genomes.

Tuesday, October 19
3:30 – 5:00 pm ET

Leveraging 150,000 whole genome sequences from the UK Biobank to transform pharmaceutical research
Moderators: Mary Helen Black, PhD, Janssen Research & Development; Mark Effingham, UK Biobank

In this session, we describe the generation of the first ~150,000 whole genome sequences from 500,000 individuals in the UK Biobank. Methods for data processing and joint variant calling at scale, as well as imputation to the entire sample set, will be described. Moreover, we will use these data to outline in detail, the distribution of ancestry and features of admixture in UK Biobank participants. We specifically highlight the assessment of short tandem repeats in the whole genome sequencing data, and the opportunity to assess the contribution of these variants to thousands of phenotypes present in the participants of the UK Biobank. Next, we provide context for investigating disease associations by comparing analytical approaches from genome-wide association to burden tests and beyond in variants identified by whole genome sequencing, with a focus on the advantages of using whole genome sequencing analysis over genotyping array alone for drug discovery. Lastly, we elucidate how such large-scale genomics data combined with the detailed phenotyping available in the UK Biobank can be used to inform drug safety studies, providing use cases that span multiple therapeutic areas and discussing their potential impact on early de-risking strategies for drug development.

Speakers:
Whole genome sequencing and variant calling in 150,119 individuals in the UK Biobank. Bjarni Halldórsson, PhD, deCODE genetics
Assessing the contribution of short tandem repeats to human disease using 150K UK Biobank Genomes. Katherine Smith, PhD, AstraZeneca
Assessing the value of whole genome sequencing in drug discovery. John Whittaker, PhD, GlaxoSmithKline
Meaningfully informing drug safety studies using data from the UK Biobank. Mary Helen Black, PhD, Janssen Research & Development

Learning Objectives:
1. Define the methods used to generate high quality whole genome sequencing data, including rare SNP, indels, and structural variants, from >150,000 individuals in the UK Biobank.
2. Highlight the contributions that short tandem repeats (microsatellites) identified by whole genome sequencing have to broader human health conditions and outcomes in a large population-based sampling.
3. Compare the value of whole genome sequencing to that of genotyping array data in large human cohorts, with application to drug discovery.
4. Describe the ways in which large-scale genomic data can be used for target liability assessment and support for de-risking strategies in drug development.

Tuesday, October 19
3:30 – 5:00 pm ET

Defining target genes in complex disease: A roadmap to precision medicine
Moderators: Laura Fachal, PhD, Wellcome Sanger Institute; Tuuli Lappalainen, PhD, New York Genome Center

Fifteen years have passed since the first genome wide association study (GWAS) was published. Thousands of loci have been identified since then, many shared across diseases, expanding our knowledge of the biology of complex traits, opening the door to tailored medicine, and even driving the discovery of new therapeutic options. However, there are still challenges to overcome, as we will discuss in this session. We will begin by exploring the most current GWAS results for Inflammatory Bowel Disease, as a model of a complex disease. In the first talk we will show how genetics, in combination with multi-omics data across different cell types, has contributed substantially to expanding our knowledge of disease biology, as well as the impact on understanding subtype specific susceptibility, prognosis and response to treatment. With the number of new GWAS studies still rising, lack of population diversity remains a common issue. This limits our ability to characterize the full genetic architecture of complex traits. To illustrate the benefits of including greater population diversity, we will focus on the human leukocyte antigen (HLA) complex, and describe the advantages of using a multi-ethnic reference panel for the discovery and determination of HLA-disease association. Another key challenge is linking the large number of non-coding variants to their target gene and relevant cell type(s). The integration of expression quantitative loci (eQTL) provides an excellent tool to define both. However, heterogeneity of effect across different cells types, and dynamic gene regulation upon different stimuli, can impact the discovery of disease associated eQTLs. We will show how evaluating expression in macrophages, upon different immune stimulation, significantly improves coupling causal variation to function. Finally, although these variants discovered through GWAS confer relatively small effects, the therapeutic relevance of their target genes is independent from their effect size on the trait. Thus, genetics has recently become a particularly useful tool to inform drug discovery, significantly increasing the likelihood of drug approval. So, in our final talk, we will explore how the results of all this work are currently being leveraged in the pharmaceutical industry. We will be describing the "allelic series" model, and how integrating molecular traits (eQTLs, protein QTLs) can help define and validate therapeutic hypotheses.

Speakers:
IBD as a model complex trait: implications for Precision Medicine and novel target identification. Judy Cho, MD, Icahn School of Medicine at Mount Sinai
Characterizing the role of HLA in immune-mediated traits via a high-resolution multi-ancestry HLA reference panel. Yang Luo, PhD, Brigham and Women's Hospital and Harvard Medical School
Genetics effects on expression upon immune stimulation in iPSC-derived macrophages enhance the discovery of putative causal disease genes. Nikos Panousis, PhD, Wellcome Sanger Institute
Human genetics and drug discovery. Robert Plenge, MD, PhD, Bristol Myers Squibb

Learning Objectives:
1. Report key findings on Inflammatory Bowel Disease, as a model of complex disease, from gene discovery to personalized medicine.
2. Illustrate the value of using a multi-ethnic reference panel to better define population specific haplogroups and enable multi-ethnic fine-mapping studies in the HLA region.
3. Examine a cutting-edge map of immune response QTLs under different conditions to facilitate the connection between GWAS signals to target genes in immune mediated diseases.
4. Summarize the most recent advances in drug discovery for immune mediated diseases lead by human genetics.

Wednesday, October 20
3:30 – 5:00 pm ET

Cell-free DNA: Biological and clinical applications
Moderators: Michael Hoffman, PhD, Princess, University of Toronto; Alexis Zukowski, PhD, University of Colorado

Extracellular DNA found in blood plasma, or cell-free DNA (cfDNA), has emerged as a minimally invasive biomarker for the detection of disease and monitoring disease progression. Use of cfDNA is routine for non-invasive prenatal testing, and its use to get a snapshot of health from a simple blood draw is growing in such disparate domains as cancer, organ transplantation, and aging. In the last several years, technological developments have enabled the use of cfDNA to examine not just genetic sequence and chromosomal abnormalities, but also the epigenomic state and active gene expression program of the originating cells. This leads to richer information that researchers and clinicians are using to understand both biology and disease. This session highlights the exciting capabilities for biological investigation and clinical diagnostics using cell-free DNA. The featured presentations cut across medical domains (cancer, aging, and obstetrics) and biomolecular properties (germline DNA sequence, somatic DNA mutations, DNA methylation, and nucleosome positioning). The studies discussed span the gamut from in vitro technology development to studies on patient cohorts. This session will demonstrate the diversity of approaches in cfDNA technology, bringing together experts and synthesizing knowledge from multiple biological, medical, and technological domains.

Speakers:

Cell-free DNA as a predictor of nucleosome positioning and a biomarker of aging. Nicola Neretti, PhD, Brown University

DNA methylation reveals tissue origins of cell-free DNA. Ruth Shemer, PhD, Hebrew University of Jerusalem

cfDNA in gastrointestinal cancers: are we ready? Aparna Parikh, MD, Massachusetts General Hospital

Cell-free DNA in the plasma of pregnant women provides snapshots of maternal, placental and fetal health. Diana Bianchi, MD, NIH

Learning Objectives:

1. Implement strategies for tissue of origin determination using cell-free DNA.
2. Evaluate differences in performance for tissue of origin determination between cell free DNA and cell free DNA methylation assays.
3. Identify the current and future applications of cfDNA technologies in gastrointestinal cancers.
4. Summarize reasons for non-reportable or false positive non-invasive prenatal testing (NIPT) results.

Wednesday, October 20
3:30 – 5:00 pm ET

N-of-1 precision medicine in the era of antisense oligonucleotide therapeutics
Moderators: Timothy Yu, MD/PhD, Boston Children's Hospital; Wendy Chung, MD/PhD, Columbia University

Precision medicine leverages the patient's genome to design therapies that results in improved outcomes. The relatively mature technology behind antisense oligonucleotides (ASOs) allows for truly personalized therapy, but requires coordination between families, health care professionals, industry, and regulatory bodies. In this session we will discuss early forays in the application of ASOs as individualized medicine. Topics to be covered include an overview of ASO biology, pediatric and adult examples of their deployment as individualized medicine, and ethical, regulatory, and patient perspectives.

The session chairs also invite you to join our companion Virtual Inspiration Lounge session which will continue the discussion from scientific, ethical, regulatory, and patient perspectives. Further details will be added to the schedule in August.

Speakers:
Antisense oligonucleotides for ultra-rare diseases: the n-Lorem experience. Stan Crooke, MD, PhD, n-Lorem
RNA-targeting treatments for Amyotrophic Lateral Sclerosis. Robert Brown, MD, PhD. University of Massachusetts Medical School
Therapeutic ASO interventions for neurodevelopmental disorders: lessons from Angelman Syndrome. Elizabeth Berry-Kravis, MD, PhD, Rush University Medical Center
Early forays in individualized genomic medicine, the milasen example & beyond. Timothy Yu, MD/PhD, Boston Children's Hospital

Learning Objectives:
1. Understand the types of mutations, diseases, and target tissues that are amenable to ASO therapeutic targeting.
2. Understand the medical/ethical/financial aspects of patient prioritization.
3. Understand the collaborative aspects and bottlenecks in advancing therapy.
4. Understand both the hopes and realistic expectations of ASO therapy for rare disease.

Wednesday, October 20
3:30 – 5:00 pm ET

Novel insights into gene-environment interactions from environmental influences on Mendelian disease phenotypes

Moderators: Kimberly McAllister, PhD, NIEHS; Charmaine Royal, PhD, Duke University

Recent advances in animal models and genomic technologies have revealed that some environmental exposures and gene-environment interactions appear to have an impact on the variable expressivity, progression, severity, and onset of some monogenic-inherited human diseases. Some potential molecular mechanisms whereby environmental risk factors have an impact on monogenic disease outcomes using Huntington's Disease (HD), Familial Parkinson's Disease (PD), and Sickle Cell Disease (SCD) as three common Mendelian disease examples will be highlighted. One presentation will describe work illustrating potential impact of pesticides on HD repeat instability. HD is caused by CAG trinucleotide repeat expansions in the HTT gene, leading to RNA/protein toxicity. Repair of oxidative DNA damage is emerging as a prominent contributor to CAG repeat instability. Data will demonstrate that pro-oxidant pesticides increase HTT CAG repeat lengths. Since many other neurological Mendelian disorders (Fragile X, myotonic dystrophy, Friedreich ataxia) are associated with unstable repeat expansion mutations, characterizing the influence of common pro-oxidant environmental exposures may provide inroads to preventing or slowing disease. A second presentation will highlight changes in manganese (Mn) biology in rodent and human stem cell-based HD models. This talk will illustrate the utility of mendelian genetic models to drive strong gene-environment interactions that tip the balance between neurological health and disease. Data elucidating the HD-Mn interactions at the level of metabolism, autophagy, and mitochondrial function will be presented. A third speaker will discuss familial PD, a neurodegenerative brain disorder characterized by selective dopaminergic cell loss that results in overt motor/cognitive deficits and is associated with a-synuclein mutations. Data will emphasize the use of the genetically tractable invertebrate Caenorhabditis elegans model to highlight the neurotoxic/neuroprotective roles of a-synuclein upon acute Mn exposure in the background of genes mutated in familial PD. A final speaker will highlight known and potential gene-environment interactions that impact SCD phenotypes, as well as ethical, social, and policy implications of gene-environment interactions research. All speakers will relate the understanding of gene-environment interactions in the context of racial and ethnic health disparities due to elevated exposures in minoritized communities.

Speakers:

Pesticides increase Huntington's Disease CAG repeat allele instability. Brandon Pearson, PhD, Columbia University

Huntington's Disease Genotype Alters Neuronal Manganese Biology and Toxicological Sensitivity to Manganese. Aaron Bowman, PhD, Purdue University

Manganese-induced Parkinsonism: Genetic insight from worms. Michael Aschner, PhD, Albert Einstein College of Medicine

Sickle Cell Disease: A gene-environment model for understanding and addressing health disparities. Charmaine Royal, PhD, Duke University

Learning Objectives:

1. Discuss possible mechanisms that are shedding new light on how environmental exposures and other environmental risk factors impact Mendelian disease outcomes, which is a significantly understudied area in the human genetics field.
2. Define the main types of state-of-the art environmental and genomic approaches that are being used to explore exposure impacts on disease pathways related to both complex and Mendelian diseases.
3. Advocate for utilizing well-established Mendelian disease models with environmental exposures to further advance the understanding of gene-environment interactions for both classic genetic disorders as well as complex human disease phenotypes.
4. Explore the role of gene-environment interactions for classic genetic disorders in the context of environmental justice concerns due to the disproportionate burden of adverse exposures - disease risk for minoritized populations.

Wednesday, October 20
3:30 – 5:00 pm ET

Global genomics and health equity: Challenges and opportunities
Moderators: Sarah Tishkoff, PhD, University of Pennsylvania School of Medicine; Catherine Tcheandjieu, PhD, Stanford School of Medicine

This session will focus on opportunities, challenges and ethical issues related to studying ethnically diverse populations to improve discovery and health equity in genomic medicine. Here we gather scientists from across the globe with experience in conducting genomic research in populations under-represented in human genetics research. Speakers will address research on genetic risk factors for medical phenotypes of particular relevance to the study populations. We will also discuss ethical, social, and legal issues (ELSI) that arise when conducting genomic research in Indigenous communities, ways in which we can achieve more inclusive and equitable research, and ensure benefit sharing. We will have four 15-minute presentations followed by a 30-minute panel discussion. Our session will start with a presentation discussing studies of pharmacogenetic variation in Indigenous peoples from South America and implications for personalized medicine in these populations. Our second speaker will describe results of a multi-ethnic genome wide association study (GWAS) of Differentiated Thyroid Cancer (DTC) in Melanesians from New Caledonia and Polynesians from French Polynesian, two populations with the highest incidence of DTC worldwide. The speaker will illustrate the impact of genetic studies of DTC risk on community health in Oceanian populations. The next speaker will follow on the promising future for genetic discovery that can be achieved by studying African populations that have high levels of genomic and phenotypic diversity. This speaker will also illustrate how the study of ethnically diverse African populations has shed light on the genetic basis of hearing impairment, resulting in identification of multiple novel genes influencing hearing loss. Our last speaker will discuss ethical perspectives and the challenges of conducting genomic research in Indigenous populations from North America, the potential benefit for personalized medicine, and the importance of creating a partnership with Indigenous communities. The panel discussion, which will include the two moderators and audience participation, will focus on how studies of ethnically diverse populations are of benefit to the global medical genetics community. We will further discuss ethical issue that arise from consequences of research that stigmatizes Indigenous communities and will touch base on principals of how to conduct research in minority and Indigenous populations in an ethical manner.

Speakers:
Addressing the claim for genomic studies of neglected populations: pharmacogenetics and actionable genotypes in Andean and Amazonian Native Americans. Eduardo Tarazona-Santos, PhD, Universidade Federal de Minas Gerais
Genetic risk factors of thyroid cancer in Oceanian population. Therese Truong, PhD, Inserm AD - Paris 11
Africa is the next frontier of novel disease genes discovery: the case of Hearing Impairment. Ambroise Wonkam, MD, University of Cape Town
Ethical perspectives and implications of implementing personalized medicine and pharmacogenomics in Indigenous communities. Katrina Claw, PhD, University of Colorado

Learning Objectives:
1. To understand why the inclusion of ethnically diverse populations in human genetics is a scientific imperative which can inform studies of risk factors for both common and rare diseases.
2. To learn how inclusion of ethnically diverse populations can promote health equity.
3. To understand the challenges related to studying populations that have cultural and societal structures different from western cultures.
4. To highlight the consequences of research that stigmatizes indigenous communities and the effect on increasing health disparities. Additionally, to better understand how to conduct research in minority and indigenous populations in an ethical manner.

Wednesday, October 20
3:30 – 5:00 pm ET

Stakeholder perspectives on ethical and social implications of using clinical polygenic risk scores through embedded ELSI research

Moderators: Noura Abul-Husn, MD/PhD, Icahn School of Medicine at Mount Sinai; Ellen Clayton, MD, Vanderbilt University Medical Center

Many polygenic risk scores (PRS) have been published with an eye towards clinical implementation. However, little work has been done on the social and ethical considerations of calculating and returning PRS, particularly across genetic ancestral backgrounds. This session reports findings from embedded ELSI studies examining social and ethical considerations of returning clinical PRS across diverse populations. The panel will advance our understanding of critical issues that must be addressed to maximize potential benefits of clinical PRS. Following an introduction to the topic, Maya Sabatello describes the views of patients, clinicians and IRB members about challenges translating PRS research into improved care and strategies to promote health equity. Broadening our understanding of variation in stakeholder views, Sabrina Suckiel highlights English- and Spanish- speaking patients' perceptions of clinical utility of PRS, preferences regarding return of information and potential barriers to uptake. The format of PRS results can impact patient and provider understanding of risk and responsiveness to corresponding recommendations. Anna Lewis discusses research on stakeholder preferences regarding various formats of return and the potential impacts on use and understanding. Finally, Ellen Clayton presents data on the role of patient education to ensure researchers understand racial/ethnic minority views on clinical PRS. Following discussion, closing remarks will highlight the utility of embedded ELSI projects within large-scale PRS or genomic studies and offer recommendations for future research. These studies, embedded in the Electronic Medical Records and Genomics (eMERGE) IV Network, were designed to inform return of actionable PRS for common complex diseases to patients and their healthcare providers.

Speakers:

The promise and pitfall of PRS for health equity. Maya Sabatello, LLB, PhD, Columbia University
Attitudes and preferences towards PRS among diverse English- and Spanish-speaking patients. Sabrina Suckiel, MS, CGC, Icahn School of Medicine at Mount Sinai
ELSI considerations for PRS reporting choices. Anna Lewis, PhD, Harvard University
Exploring Minorities' Attitudes about PRS. Ellen Clayton, MD, Vanderbilt University Medical Center

Learning Objectives:

1. Describe key ethical and social implications associated with clinical PRS implementation.
2. Learn about the perspectives of key stakeholders, including patients of diverse backgrounds, clinicians, and IRB members, regarding the integration and uptake of PRS in healthcare settings.
3. Understand factors that should inform communication of clinical PRS to patients and providers.
4. Identify areas for future study regarding the utility, benefits, and challenges associated with clinical PRS implementation.

Thursday, October 21
3:30 – 5:00 pm ET

Workforce diversity in genomics: Equity and the meaning of inclusion
Moderators: Sandra Soo-Jin Lee, PhD, Columbia University; Stephanie M. Fullerton, PhD, University of Washington

A resounding call for increased workforce diversity has been made in the genomics research community in recent years (Green et al. 2020; Channaoui et al. 2020). Recognizing the lack of diversity in both research participants and in the genomics workforce, workforce diversity initiatives strive to train and retain diverse members of the scientific community such that scientific fields are more inclusive and better represent racial, ethnic, sexual, gender minority, and differently abled groups. The NHGRI 2020 Strategic Vision, for instance, articulates how building a diverse genomics workforce will be a key priority "to promote workforce diversity, leadership in the field, and inclusion practices." A broad literature demonstrates the lack of diversity among NIH funded investigators, even as research has demonstrated that researchers from underrepresented groups develop novel scientific projects at higher rates (Hofstra et al. 2020). This panel will examine workforce diversity initiatives and practices that aim to redress inequities that have excluded underrepresented and communities of color from the genomics leadership and workforce more broadly. Drawing on empirical cases and the experiences and perspectives of researchers and program leaders on initiatives aimed at increasing diversity and inclusion in the field, this panel will discuss how definitions of diversity, commitments to diverse experiences, distribution of resources and infrastructures, and professional networks directly impact equitable diversification of the workforce. This panel will consider how an equity framework can be brought to bear on questions of what workforce diversity efforts can and should accomplish, who should be responsible for such initiatives, and what sustainable/lasting commitment to workforce diversity means for the genomics community moving forward.

Speakers:
Bringing change to the genomics workforce. Vence Bonham, JD, NIH/NHGRI
"True diversity is when you start to see inclusion": Centering Equity in Precision Medicine Workforce Diversity Initiatives. Sandra Soo-Jin Lee, PhD, Columbia University
Paving a road to increase equity for Indigenous scientists in genomics research. Nanibaa' Garrison, PhD, University of California, Los Angeles
Diversity is bigger than this: why we must reconceive "diversity" in the context of the genomics workforce. Consuelo Wilkins, MD, Vanderbilt University Medical Center and Meharry Medical College

Learning Objectives:
1. Identify how workforce diversity is conceptualized in genomics.
2. Describe current initiatives to increase workforce diversity in genomics.
3. Critically evaluate the barriers of specific approaches to increasing workforce diversity in basic and clinical research.
4. Identify the factors related to multi-disciplinary teams that impact workforce diversity.

Thursday, October 21
3:30 – 5:00 pm ET

Technologies for optimizing impact of precision animal models for variants of uncertain significance or therapeutic development

Moderators: Deeann Wallis, PhD, University of Alabama at Birmingham; Elizabeth Bhoj, MD/PhD, Children's Hospital of Philadelphia

Clinical application of modern sequencing technologies has identified large numbers of variants of uncertain significance (VUS). While computational assessment can predict the functional outcome, functional assays and model systems remain the gold- standard. However, generation of variant-specific models is relatively low throughput as it is extremely time consuming and can be quite costly. In addition, limited access by individual investigators to the high-throughput approaches needed for testing gene function in different genetic contexts and guiding principles to choose the best model system for a particular application are further impediments. Thus, ways to prioritize and streamline VUS and models are required and are the focus of this session. Several Centers for collaborative research projects that link current personalized medicine efforts in human subjects with advances in animal genomics and technologies for genetic manipulation have received NIH funding to create pipelines for the generation of precision animal models and distribution of model resources and related services to the biomedical community. Assessments of VUS begin with the utilization of novel bioinformatics algorithms for annotation, classification, prioritization, interpretation, and selection of variants and model organisms, as well as prioritization of drug targets, and facilitation of collaborations between clinicians and scientists. The ability to produce animals with specific genetic modifications and to replace specific cells and tissues in a variety of species has recently been enhanced dramatically by the development of new technologies including the humanization of flies and GFP-tagging of proteins of interest. Transcriptomics can be utilized to uncover both molecular functions and drug repurposing; and automated imaging approaches in fish can also be used for increased phenotyping throughput and screening. Finally, CRISPR/Cas9 editing for generation of precision alleles in F0 mouse embryos and direct phenotyping in F0 (“founder”) animals can be used to expedite phenotyping. Notably, these advances can democratize therapy development since in rare disease there's so much inequity in which disease gets prioritized. Overall, we anticipate that these technologies will have a significant impact in our ability to increase the utility of the models that are generated and their application in therapeutics development.

Speakers:

Application of data science and computational biology approaches: from variant impact to therapeutic selection. Liz Worthey, PhD, University of Alabama at Birmingham

Approaches Used in Fruit flies for the Diagnosis and Discovery of Rare Undiagnosed Diseases. Hugo Bellen, DMV PhD, Baylor College of Medicine

From gene discovery to therapeutic drug targets: the zebrafish suite of in vivo tools to study human genetic disease. Kamal Khan, PhD, Lurie Children’s Hospital of Chicago

Mouse model platforms for precision genetics: from variant validation to preclinical applications. Steve Murray, PhD, The Jackson Laboratory

Learning Objectives:

1. Awareness that multiple Centers exist such that variants or models may be nominated by the community.
2. Understand computational integration to streamline and prioritize workflow.
3. Identification of factors that prioritize or deprioritize VUS/models.
4. Introduction of new technologies and therapeutic advancements.

Thursday, October 21
3:30 – 5:00 pm ET

Expanding the frontiers of congenital disorders of glycosylation

Moderators: Fernando Scaglia, MD, Baylor College of Medicine; Christina Lam, MD, University of Washington and Seattle Children's Hospital

The aim of this session is to expand the known frontiers of congenital disorders of glycosylation (CDG), an umbrella term for a rapidly expanding group of rare genetic disorders due to defects in a complex cellular process known as glycosylation. The discovery of novel types of CDG and the underlying molecular genetic defects will be reviewed. The interpretation of data obtained by metabolomics, like glycomics, where the presence of a specific glycan sub-fraction can lead to pattern recognition and the direct diagnosis of certain types of CDG and better definition of the human glycome will be discussed. Despite the difficulties encountered in generating efficient in vivo models, the session will illustrate the progress on animal models for CDG that are necessary for a better understanding of the pathophysiological mechanisms underlying CDG and to assess safety and efficacy of compounds in the stage of pre- clinical testing. Finally, new therapeutic avenues for CDG that have been developed or are currently being evaluated in clinical trials will be presented. In summary, this session aims to focus on the current state of the art research on the discovery of novel types of CDG and their genetic bases, ascertainment of new types of CDG and validation of genomic variants by the use of functional glycomics, the development of mouse models, and the search for new therapeutic approaches in this group of disorders.

Speakers:
The quest to identify novel types of CDG and their molecular genetic bases. Hudson Freeze, PhD, Sanford Burnham Prebys Medical Discovery Institute
Functional Glycomics, a robust tool of pattern recognition in the diagnosis of CDG. Richard Cummings, PhD, Harvard Medical School, Harvard University
Novel Mouse Models for CDG and the exploration of gene therapy for PGM1-CDG. Kent Lai, PhD, University of Utah
Bringing CDG therapies from the bench to the bedside. Eva Morava, MD, Mayo Clinic Rochester

Learning Objectives:

1. To review the discovery and molecular basis of novel types of CDG.
2. To illustrate the relevance of glycomics in pattern recognition and direct diagnosis of certain types of CDG.
3. To discuss the progress on animal models for CDG that are necessary for a better understanding of the pathophysiological mechanisms underlying and to assess safety and efficacy of compounds in pre-clinical testing.
4. To recognize new therapeutic avenues for CDG that have been developed or are currently being evaluated in clinical trials.

Thursday, October 21
3:30 – 5:00 pm ET

Cross-ancestry genomic research: Time to bridge the gap
Moderators: Sandra Sanchez-Roige, PhD, UCSC; Hae Kyung Im, PhD, The University of Chicago

The success of genome-wide association studies (GWAS) in humans have yielded a wealth of clues about the molecular basis of many common human diseases. In addition, polygenic risk scores (PRS) for a variety of traits are increasingly becoming accurate enough to be useful for clinical practice, realizing the longstanding goal of personalized medicine. However, data collection continues to be predominantly imbalanced towards individuals of European ancestry, and it is abundantly clear that methods developed in one human ancestry group do not perform well in other ancestry groups, limiting their utility and exacerbating already severe health disparities. The speakers in this session will introduce recent efforts to level ancestry imbalance in genomic research, including the formation of large collaborative efforts and the development of novel statistical methods.

Speakers:
Polygenic transcriptome risk scores improve portability of polygenic risk scores across ancestries. Yanyu Liang, MS, The University of Chicago
PRS-CSx: Improving Polygenic Prediction in Ancestrally Diverse Populations. Tian Ge, PhD, Harvard Medical School
The role of local ancestry and DNA methylation in gene expression in African Americans. Minoli Perera, PhD, Northwestern University
Improving genetic translation across LatinX populations. Janitza Montalvo-Ortiz, PhD, Yale University

Learning Objectives:
1. Recognize the need to reduce health inequities that are of increasing concern to geneticists and the general public.
2. Share novel methods that enhance translation of genomic findings across populations.
3. Report results of genetic association analyses from ethnically diverse cohorts.
4. Discuss recent diversifying efforts (e.g. formation of novel consortiums) that will ensure that the benefits of genetic findings (e.g., personalized medicine) are shared beyond European populations.

Thursday, October 21
3:30 – 5:00 pm ET

Medical and evolutionary insights into human resistance against pathogens
Moderators: Tábita Hünemeier, PhD, University of São Paulo; C. Eduardo Guerra Amorim, PhD, California State University, Northridge

As humans populated all regions of the globe, they were exposed to different environments and pathogens. Evolutionary events such as migrations, genetic drift, and natural selection have shaped human genetic diversity and the organism's defense against pathogens and disease susceptibility. In this session, we bring together four scholars whose recent work has focused on understanding the causes of genetic diversity in humans and its consequences to interindividual variation in response to pathogens. We will discuss recent efforts to analyze biobanks for infectious diseases and examine the development of new methodological frameworks to characterize the evolution of genetic variants associated with disease risk and severity. Rodrigo Barquera (Max Planck Institute for the Science of Human History) introduces his work on human leukocyte antigen (HLA) peptide-binding patterns for different viruses among populations. Amy Goldberg (Duke University) presents her work demonstrating that adaptation to malaria has dramatically shaped genetic diversity in Cabo Verde (Africa) and South America during the past 500 years, introducing her new methods for studying natural selection in admixed populations. Alexandre Pereira (University of São Paulo; Harvard Medical School) discusses his work on genetic susceptibility to Chagas disease in admixed populations. Alessandra Renieri (University of Siena) presents her work with the GEN-COVID Multicenter Study, which leverages common and rare genetic variants in humans to untangle host genetics complexity in COVID-19 cases with diverse outcomes. The talks will be followed by a 20-minute panel discussion with all speakers and the participation of the audience.

Speakers:
Immunogenetics beyond clinics: can we be Heroes, or are we Absolute beginners? Rodrigo Barquera, PhD, Max Planck Institute for the Science of Human History
Evolutionary perspectives on human adaptation to malaria. Amy Goldberg, PhD, Duke University
Machine Learning approach to untangle host genetics complexity in COVID-19. Alessandra Renieri, MD, University of Siena
Genomic Medicine in Chagas Disease. Alexandre Pereira, MD/PhD, Harvard Medical School

Learning Objectives:
1. To understand the evolutionary forces shaping the immune response to pathogens.
2. To elucidate how human population history affects genetic diversity associated with resistance against pathogens and other biomedical traits.
3. To discuss new methods and approaches to characterize recent and ongoing selection caused by the interaction between human and pathogens.
4. To gain medical insights into the dynamics of neglected diseases and the current COVID-19 pandemics.

Friday, October 22
3:30 – 5:00 pm ET

Gatekeeping genetics: Towards a more diverse, just, and inclusive research enterprise

Moderators: Daphne Martschenko, PhD, Stanford University School of Medicine; Markia Smith, PhD Candidate, UNC Chapel Hill School of Medicine

Science answers the questions researchers ask it. The research enterprise is designed to emphasize the voices internal to it over external voices. This form of gatekeeping loses the richness of diverse perspectives, shaping approaches and priorities in research and the discovery process. While forms of gatekeeping are woven into the fabric of scientific research broadly, the field of human genetics is particularly susceptible to the perils of gatekeeping given a history of research (mis)use and (mis)interpretation. This session interrogates the ways in which we, as participants in the field of human genetics, might engage in and respond to various forms of complicity in gatekeeping. The overarching objective of this session is to discuss how to make the field of human genetics more diverse, just, and inclusive and to understand and remedy the current structures and social forces that keep the gates of the field closed to too many. It does so by first bringing together diverse stakeholders in the field to consider gatekeeping in: (1) the recruitment and retention of researchers of color in genetics; (2) the inclusion of communities who have been most harmed by the antecedents of current research in human genetics; (3) the academic publishing enterprise. However, this session moves beyond a simple discussion of whether and how gatekeeping perpetuates inequality in human genetics to explore, along a number of dimensions, the social and ethical implications of gatekeeping in genetics. Alongside audience members, speakers will engage in a productive dialogue on frameworks, practices, and priorities to address gatekeeping in our field. In summary, this session asks:

1. What are the different forms of gatekeeping in human genetics? Why do they exist and what are our individual and collective complicities in the maintenance of gatekeeping?
2. What are the implications of gatekeeping? How does it affect the creation and communication of research?
3. What are frameworks, practices, and priorities to address gatekeeping?

Speakers:

#Bootless in Genetics. Russell Ledet J, PhD, Tulane University School of Medicine

Opening the gates: a push for the inclusion of Black people in genomic medicine. Markia Smith, PhD Candidate, UNC Chapel Hill School of Medicine

Access and Availability of Genetic Testing for Prenatal Patients. Deanna Darnes, CGC, Fetal Care Center

From gatekeeping to partnership: How journals can contribute to a more equitable scientific process. Catherine Potenski, PhD, Nature Genetics

Learning Objectives:

1. Understand the ways in which the field of human genetics acts as a gatekeeper to diversity, equity, and inclusion.
2. Analyze the social and ethical implications of gatekeeping in human genetics research, including the implications of gatekeeping for the production of robust and rigorous scientific research.
3. Identify and apply practical and constructive avenues for facilitating the creation of a more diverse, just, and inclusive research enterprise in human genetics.
4. Consider individual complicities and responsibilities as stakeholders in human genetics research who are interested in innovating responsibly and supporting human flourishing in a field with an ugly history.

Friday, October 22
3:30 – 5:00 pm ET

Global resources for precision medicine research
Moderators: Joshua Denny, MD, NIH; Latrice Landry, PhD, Harvard Medical School

Research in human genetics, genomics, and precision medicine is entering a new era of opportunity for discovery with release of large phenotype- and genotype-rich data resources such as the NIH All of Us Research Program and UK Biobank. Expanding global opportunities further are robust efforts such as the International HundredK+ Cohorts Consortium (IHCC) to coordinate large cohort studies and promote a global platform for biomedical research, and the Global Alliance for Genomics and Health (GA4GH) that is establishing technical standards and a policy framework necessary to enable data sharing across nations. Speakers in the session will illustrate the potential of these initiatives to provide novel insights into population-level components of risk and wellness, as well as individual genotypic, phenotypic, and environmental influences, that form the basis of precision medicine. The research opportunities are only now becoming feasible with the scale presented by these global resources, in both human genome data and multi-layered phenotypic and behavioral data. Of great importance will be the addition of substantial and diverse data drawn from communities historically underrepresented in biomedical research. In addition to providing early results, including insights into COVID-19 etiology, current status and projections for scale and data content will be presented, as well as principles and procedures for data access and in situ analyses. To take full advantage of the growing collection of cohorts and population studies requires cooperation, within and across borders, in the form of common interoperable technical standards for data format as well as common terminologies and ontologies; scalable methods to enable data access and track researcher identity; cloud computing models and approaches for federated analysis; and shared policy and ethical principles. The efforts to create a linked and fluid resource for global researchers to discover the data and utilize it for advancing global health will be described, with an emphasis also on the substantially enhanced diversity of genetic ancestry, sociological, and environmental variables in the data as well as diversity expected in those accessing it.

Speakers:
NIH's All of Us Research Program: Diversity and Scale in Precision Medicine Research. Joshua Denny, MD, NIH
UK Biobank in 2021 and Beyond. Naomi Allen, MD, PhD, UK Biobank
The IHCC Experience Bringing Cohorts Data Together to Advance Precision Health Research Around the Globe. Laura Lyman Rodriguez, PhD, Patient-Centered Outcomes Research Institute (PCORI)
GA4GH Standards to Enable Global Access and Interoperability of Data to Inform Precision Health. Heidi Rehm, PhD, Massachusetts General Hospital and Broad Institute of MIT and Harvard

Learning Objectives:
1. How are large national population studies such as the All of Us Research Program and the UK Biobank structuring data and enabling access to investigators to enable discovery from diverse populations, inclusive of all ancestral groups?
2. How are global resources for precision medicine research being optimized for new discovery?
3. Nations/organizations have invested substantially in establishment of data-rich cohorts globally; how are policies/technical standards being developed to allow linkage and data sharing across the many cohorts, enhancing the potential for discovery?
4. With rapidly advancing technology in genomics and in phenotypic data collection, what are emerging opportunities to investigate components of disease and wellness, with contributions from genotype, environment, and lifestyle?

Friday, October 22
3:30 – 5:00 pm ET

Nonsense-mediated decay: A double-edged sword in cancer and genetic diseases
Moderators: Zeynep Coban Akdemir, PhD, UTHealth School of Public Health; Stephen Song Yi, PhD, The University of Texas at Austin

Nonsense-mediated decay (NMD), an evolutionarily conserved mRNA surveillance mechanism, plays a dual role in mammalian cells: maintenance of normal gene expression and degradation of premature termination codon (PTC)-bearing aberrant transcripts resulting in loss-of-function (LoF) alleles. However, not all PTCs are created equal. In mammalian cells, PTCs located in the final exon or the last 50-55 base pairs (bp) of penultimate exon may not elicit NMD, which can lead to the production of truncated or altered proteins. Approximately one-third of known pathogenic variants in cancer and genetic diseases are PTCs whose disease outcome is modulated by NMD. Overall, this suggests that NMD inhibition, attenuation, or activation may be an effective therapeutic strategy to treat genetic diseases. However, identification of diseases and individuals that may benefit from NMD inhibition or activation will require a thorough understanding of the impact of NMD on normal or aberrant gene expression. This session will highlight current research into the role of the NMD pathway in reprogramming of gene expression in response to external and genetic cues during development and in genetic diseases, where it alters disease outcome. The first speaker will introduce the topic with a special emphasis on NMD mechanism and its role in the maintenance of normal gene expression and misregulation of the NMD pathway by the fragile X syndrome protein, FMRP. Our next speaker will describe the role of NMD factors during development and their tissue-specific downstream targets. The following speaker will highlight current research about NMD-specific disease genes, the genes that are causative of Mendelian disease traits only when their transcripts escape from NMD through a potential gain-of-function (GoF) mechanism. And the final speaker will describe the role of NMD-eliciting poison exons, exons that trigger NMD when included in a transcript, in cell growth and tumorigenesis.

Speakers:
Loss of the fragile X syndrome protein FMRP results in misregulation of nonsense-mediated mRNA decay. Tatsuaki Kurosaki, PhD, University of Rochester Medical Center
The NMD Factor UPF3B Shapes RNA Metabolism During Mammalian Neural Development. Miles Wilkinson, PhD, University of California, San Diego
Gain-of-Function MN1 Truncation Variants Cause a Recognizable Syndrome with Craniofacial and Brain Abnormalities. Noriko Miyake, MD, PhD, Yokohama City University
RNA isoform screens uncover the essentiality and tumor-suppressor activity of ultraconserved poison exons. James Thomas, PhD, Fred Hutchinson Cancer Research Center

Learning Objectives:
1. Describe the role of nonsense-mediated decay (NMD) in cancer and genetic diseases.
2. Discuss NMD inhibition, activation or attenuation as a possible therapeutic strategy.
3. Review the role of NMD factors during development and homeostasis of normal gene expression.
4. Evaluate the impact of NMD on RNA splicing related to tumorigenesis.