ASHG 2023 Invited Sessions (as of August 2023)

Friday, November 3, 8:30 – 10:00 am

The ENCODE consortium: 2003 – 2023

Moderators: Timothy Reddy, PhD, Duke University; Carolyn Hutter, PhD, National Institutes of Health

Session Type: Scientific/Education
Topic: Genetic, Genomic, and Epigenomic Resources and Databases
Track: Basic or Translational Research
Audience: Researchers

The Encyclopedia of DNA Elements (ENCODE) Project launched in 2003 with the long-term goal of developing a comprehensive map of functional elements in the human genome and sharing that map and the supporting data and analyses freely with the research community. Over the past 20 years, ENCODE has contributed to changes in the methods and understanding of genome biology. What started in 2003 with a focused analysis of 1% of the human genome has now expanded to >17,000 genome-wide experimental analyses and hundreds of thousands of computational analyses across a wide range of primary tissues, cells, and cell states. The final phase of ENCODE culminates with substantially expanding the diversity of cells and tissues with genome-wide regulatory information, resolving regulatory element activity to specific DNA sequences and individual cells, systematically connecting regulatory elements to target genes, revealing key events in production of mRNA molecules from activation to degradation, reporting the dynamics of regulatory element activity across diverse systems, advancing genome-wide functional studies of regulatory element activity, and measuring the effects of changes in DNA sequence on changes in regulatory activity in evolution and disease. This session will present the full scope of ENCODE, with a particular focus on findings from the final data generation phase of the project. The session will start with an overview summarizing how ENCODE evolved with and helped shape advances in genomics over the past two decades. The presentation will include consideration of some of the limitations and controversies that arose during the project and how ENCODE had taken on those challenges. The second presentation will describe the ENCODE Encyclopedia that cohesively organizes and presents all ENCODE data and annotations, with a particular focus on components that are new to the final phase of ENCODE. The third presentation will highlight recent efforts using ENCODE to predict the functional effects of genetic variants. The final speaker will add an international perspective on the global reach of the ENCODE project. The session will end with a wide-ranging panel discussion on how ENCODE data and resources can enable future scientific discoveries, lessons learned for future biomedical research consortia, and personal stories from diverse perspectives about the benefits and challenges of participating in such consortia.

Speakers:

The arc of ENCODE: 20 years of insight into genomic elements. Barbara Wold, PhD, California Institute of Technology

Using the ENCODE encyclopedia to better understand gene regulation. Jill Moore, PhD, University of Massachusetts Chan Medical School

Prioritizing variants for disease-related function using ENCODE encyclopedia. Kushal Dey, PhD, Memorial Sloan Kettering Cancer Center

EpiATLAS – a reference for human epigenomic research. Martin Hirst, PhD, University of British Columbia

Friday, November 3, 8:30 – 10:00 am

Use of race, ethnicity, and ancestry as population descriptors in genetics and genomics research
Moderators: Aravinda Chakravarti, PhD, NYU School of Medicine; Charmaine DM Royal, PhD, Duke University

Session Type: Ethical, Legal, and Social Issues
Topic: Genetic Counseling, ELSI, Education, and Health Services Research
Track: Basic or Translational Research; Diversity, Equity, and Inclusion; Ethical, Legal, and Social Issues
Audience: Researchers

In this session, members of the study committee will highlight and discuss the consensus report from the National Academies of Sciences, Engineering, and Medicine (NASEM) on the benefits and challenges to the use of race, ethnicity, ancestry, and other population descriptors in genetics and genomics research. The report, released in March 2023, describes the current use of population descriptors, best practices for using them in research in the future, and strategies for implementing the recommendations in the report.

Speakers:

Human population genetics perspective. John Novembre, PhD, University of Chicago

Social science perspective. Ann Morning, PhD, New York University

Community engagement perspective. Sandra Soo-Jin Lee, PhD, Columbia University

Human genetics researcher/journal editor perspective. Michael Bamshad, MD, University of Washington

Friday, November 3, 8:30 – 10:00 am

Can we promise precision medicine to all?
Moderators: Debra Murray, PhD, Baylor College of Medicine; Charles Rotimi, PhD, National Institutes of Health

Session Type: Diversity, Equity, and Inclusion
Topic: Genetic Counseling, ELSI, Education, and Health Services Research
Track: Diversity, Equity, and Inclusion
Audience: Researchers

Can the promise of precision medicine be achieved when essential research discoveries and clinical realities are unavailable for underrepresented groups? Twenty-first-century technologies and the pace of genetics and genomics discoveries hold the promise for precision medicine. As the world emerges from a pandemic that brought to light the realities of health disparities and inequalities in communities historically marginalized, we must ask how this promise can be realized. Well-known, trusted tools used in genomics reveal grave disparities in the practice of genomic medicine. Popejoy and Fullerton (2016) found that GWAS, the tool used to determine genetic factors in common diseases, samples are 3% African ancestry and less than 1% Hispanic/Latino/a. Carrier screening is another area where databases used to define clinical practice guidelines are made up of predominantly European cohorts. These and other significant disparities exist in a precision medicine era nestled in systemic racism where persistent bias dictates the use of race as a biological construct. The panel will introduce studies that enhance understanding of the disparities preventing precision medicine for all and genetic medicine topics necessary to ensure health equity for communities underrepresented in the genomic revolution. Speakers will discuss challenges such as inequitable genetic testing practices in reproductive medicine, historical lack of representation in biomedical research, and significant disparity in access to genomic care for low-income families. The panelists will offer potential solutions such as pan-ethnic expanded carrier screening (ECS) for many conditions regardless of self-reported race or ethnicity, project GIVE (Genetic Inclusion by Virtual Evaluation) that aims to simplify patient pathways and reduce the time to diagnoses for clinical decision-making in a medically underserved pediatric population, how the All of Us program enrolled 587,000 people, and the Biorepository and Integrative Genomics (BIG) Initiative with over 13,000 DNA samples, 45% African American (self-report), success is from groups that highly value community transparency, input, feedback, and genomics education. These solutions will show the importance of increasing the participation of individuals from ancestrally diverse backgrounds to ensure that clinical translation of genomic science will benefit all people and help to level the health equity playing field for all.

Speakers:

A common vision of accelerated genomic research discovery: 100,000 genomes and the BIG Initiative. Chester Brown, MD, PhD, University of Tennessee Health Science Center

The role of All of Us to recruit a large diverse participant pool. Karriem Watson, DHSc, MS, MPH, National Institutes of Health

Project Genetic Inclusion by Virtual Evaluation. Seema Lalani, MD, Baylor College of Medicine

Equitable care in carrier screening. Aishwarya Arjunan, MS, MPH, CGC, CPH, GRAIL

Friday, November 3, 8:30 – 10:00 am

Does size matter? Changing the rules of human genetics with miniproteins
Moderators: John Prensner, MD/PhD, University of Michigan; Anne-Ruxandra Carvunis, PhD, University of Pittsburgh

Session Type: Scientific/Education
Topic: Genetic, Genomic, and Epigenomic Resources and Databases
Track: Basic or Translational Research
Audience: Researchers

The human genome is conventionally divided into the protein-coding genes, which number around 20,000, and the non-coding genome, which constitutes over 98% of DNA sequences. Yet this distinction may not be so sharply defined. It is now known that the ribosome ubiquitously translates thousands of non-canonical open reading frames (ORFs), which represent a new category of RNA translation of miniproteins or small peptides. Despite their abundance, these ORFs have remained largely unannotated and therefore unstudied. Recently, technological advances in next-generation sequencing of ribosome-bound RNA fragments (termed ribosome profiling) and mass spectrometry identification of translated peptides found on the HLA antigen system (termed immunopeptidomics) have provided unbiased approaches to measure their presence and dysregulation in disease. Investigations of non-canonical ORF functional biology are revealing that many are important biological players that may enrich our knowledge of disease pathogenesis. In light of this, ongoing efforts are now beginning to incorporate non-canonical ORFs into standardized analyses of whole genome sequencing for human genetic diseases. Yet, the function of most non-canonical ORFs is unknown, and real challenges remain on how to interpret nucleotide variants found within these regions of potential protein translation. Finally, the extent to which non-canonical ORFs and the miniproteins they may encode will expand clinical medicine and disease treatment options remains to be determined. In this session, we will provide expert presentation and commentary on non-canonical ORFs. We discuss the latest research on non-canonical ORFs, efforts to incorporate them into disease studies via their annotation in the human genome, and the interpretation of disease variants found within non-canonical ORFs. We will also discuss the technological and therapeutic innovations occurring for miniprotein-based therapeutics in the industry setting, where such work has been pioneered. This session will include several core learning points emphasizing the following questions: 1. What are non-canonical ORFs and how are they detected? 2. How are non-canonical ORFs being annotated in the human genome? 3. What is the interpretation of genetic disease variants found in non-canonical ORFs? 4. How is the study of non-canonical ORFs expanding disease treatment options?

Speakers:

What are non-canonical open reading frames and how are they detected? Thomas Martinez, PhD, University of California Irvine

Annotation of non-canonical open reading frames to advance human genetics research. Sebastiaan van Heesch, PhD, Princess Maxima Center

The role of non-canonical open reading frames in Mendelian disease. Anne O'Donnell-Luria, MD, PhD, Boston Children's Hospital/Broad Institute

Non-canonical open reading frames in the clinic: Advancing bench-to-bedside efforts. Vinidhra Mani, PhD, Flagship Pioneering

Friday, November 3, 8:30 – 10:00 am

Understanding human genetic variation through the lens of germ cell biology
Moderators: Martin Breuss, PhD, University of Colorado Anschutz Medical Campus; Anne Goriely, PhD, University of Oxford

Session Type: Scientific/Education
Topic: Evolutionary and Population Genetics
Track: Basic or Translational Research
Audience: Researchers

Defining the basic mechanisms by which new mutations are introduced in our genomes is fundamental to our understanding of evolution, genome biology, and genetic disease. Over the last two decades, the systematic implementation of next-generation sequencing has provided an unbiased view of the landscape of 'de novo' mutations. The analysis of acquired variants from paired tumor-normal samples defined so-called 'mutational signatures', enabling the inference of tissue or exposure-specific mutational mechanisms. Likewise, whole-genome sequencing analysis of mother-father-child family trios concurs that we all acquire a small but consistent number of ~60 new single nucleotide variants at each generation. These data have also shown that germline biology and sexual dimorphism play a key role in controlling germline mutation rates. For instance, ~80% of de novo small variants (i.e., single nucleotide variants or small insertions/deletions) detected in offspring are of paternal origin, and their number increases with paternal age at a rate of approximately two novel mutations per year. Yet, little is known about how DNA damage and repair or cellular turnover in the germline controls mutation rates across generations. Over the last few years, novel sequencing technologies, computational resources, and advanced theoretical models have enabled the study of mutations directly within their tissues (or even single cells) of origin. We know now that all 'normal' tissues contain a surprisingly large number of clonal mutations, highlighting the complexity of the genome of multicellular organisms and confirming that intrinsic mutational rates are much lower in the germ cell lineage than in somatic tissues. The speakers of this session will summarize some of these recent insights, including the detection of neutral and pathogenic variants from bulk and micro-dissected samples, the observed rates of mutation across different tissues, the role of DNA damage and repair in this process, and how meiotic recombination shapes and amplifies genome variation and speciation. These recent advances raise new questions and hypotheses such as: what are the cellular mechanisms constraining mutation rates in germ cells? Which factors (e.g., gender, age, mutagenic exposure, or genetic background) influence germline mutation rates? Can we leverage these insights to improve or predict health outcomes? This session will provide a foundation to address these and other questions in the future.

Speakers:

The mutational landscape and clonal dynamics of male germline cells. Raheleh Rahbari, PhD, Wellcome Trust Sanger Institute

Modeling the interplay of DNA damage and repair helps to identify key parameters of human mutagenesis. Molly Przeworski, PhD, Columbia University

Recombination and its evolution drive diversity in mammals, and beyond. Simon Myers, PhD, University of Oxford

Clonal and non-clonal genomic mosaicism in sperm impact the health of the next generation. Xiaoxu Yang, PhD, University of California San Diego

Friday, November 3, 8:30 – 10:00 am

The nature of nurture: The importance of modelling indirect genetic effects in large-scale genetic studies
Moderators: David Evans, PhD, University of Queensland; Matthew Keller, PhD, University of Colorado Boulder

Session Type: Scientific/Education
Topic: Statistical Genetics and Genetic Epidemiology
Track: Basic or Translational Research
Audience: Researchers

Indirect genetic effects occur when the genotype of an individual affects the trait of another (typically related) individual. In the context of human genetic studies, failure to correctly account for the presence of indirect genetic effects may bias estimates of direct genetic effects, heritability and genetic correlation, and lead to spurious results in downstream polygenic score and Mendelian randomization studies. Conversely, estimating indirect genetic effects accurately can shed light on critical biological, social and environmental processes that may vary across population groups. In this session, we argue for the necessity of accounting for indirect genetic effects in genetic studies and discuss some of the latest breakthroughs in the development and application of statistical methods that explicitly model such effects in large-scale genetic studies of common complex traits and diseases. This includes an overview of the importance of modelling indirect genetic effects using family-based genetic studies and the opportunities afforded by utilizing such study designs, a new statistical method that increases the power of locus detection in GWAS meta-analyses of traits influenced by indirect genetic effects, a new approach that determines whether indirect genetic effects on offspring's educational attainment truly represents the effect of parenting behaviors (i.e. "genetic nurture"), and finally, application of an approach that partitions genetic variance into direct and indirect components (i.e. via relatedness disequilibrium regression) to socially patterned childhood mental health phenotypes in 25,000 genotyped parent-offspring trios from the Norwegian Mother, Father, and Child Cohort Study. We discuss the assumptions and limitations associated with each of the above study designs and highlight the importance of future investigations examining the degree to which indirect genetic effects generalize to population groups other than European ancestry and the opportunities afforded by investigating indirect effects in these populations.

Speakers:

The importance of collecting close relatives and family members in future large-scale genetic studies. Gibran Hemani, PhD, University of Bristol

Direct and INdirect effects analysis of Genetic lOci (DINGO): A simple method to increase the power of locus discovery in GWAS meta-analyses of traits influenced by indirect genetic effects. Liang-Dar Hwang, PhD, University of Queensland

Do within family genetic associations reflect genetic nurture? Michel Nivard, PhD, VU Amsterdam

Counteracting direct child and indirect parental genetic effects on childhood mental health. Rosa Cheesman, PhD, University of Oslo

Friday, November 3, 8:30 – 10:00 am

Finding NEMO: Novel Enhanced Model Organism/Organs-on-chips platforms for translational genomics research
Moderators: Joseph Hacia, PhD, University of Southern California; Wedad Fallatah, PhD, Kennedy Krieger Institute, Johns Hopkins University

Session Type: Scientific/Education
Topic: Genetic, Genomic, and Epigenomic Resources and Databases
Track: Basic or Translational Research
Audience: Researchers

Clinical whole genome sequencing has enhanced the medical community's ability to identify people with genomic disorders at earlier timepoints, in some cases prior to irreversible damage to tissues and organs. This can allow access to previously inaccessible early therapeutic windows and maximize the potential benefits of rationally designed therapeutic interventions. Nevertheless, there have been limitations in the availability of models tailored for evaluating targeted approaches, such as oligonucleotide-based and gene editing strategies, that require the context of the human sequence. Here, we will review recent progress and unpublished data relevant to developing next-generation animal and organs-on-chips models that better reflect molecular mechanisms of human diseases and enhance the evaluation of therapeutic hypotheses. Our first presentation will discuss the application of emerging genome-editing technologies to generate next-generation humanized mouse models. Our second presentation will discuss natural variation and disease-susceptibility alleles in captive non-human primate (NHP) populations and the use of genome editing to develop NHP models of Mendelian disorders. Our third presentation will focus on applications of genome editing to generate swine models for human diseases and xenotransplantation. Our final presentation will discuss transformative tissue-chip technologies as platforms for evaluating therapeutic hypotheses and testing targeted interventions prior to clinical trials. Collectively, these diverse platforms will enhance translational genomics efforts to explore molecular pathomechanisms of genomic diseases and evaluate therapeutic hypotheses as a precursor to their potential testing in clinical trials.

Speakers:

Novel genomic engineering technologies for developing next generation mouse models of genomic diseases. Aamir Zuberi, PhD, The Jackson Laboratory

Natural and genetically engineered non-human primate models of genomic and genetic disorders. Samuel Peterson, PhD, OHSU

National Swine Resource and Research Center for translational genomic research. Randall Prather, PhD, University of Missouri

Organs-on-chips for translational genomic research. Passley Hargrove-Grimes, PhD, National Institutes of Health

Friday, November 3, 8:30 – 10:00 am

Genetic diagnosis of severe fetal and newborn conditions: Opportunities and challenges
Moderators: Svetlana Yatsenko, MD, University of Pittsburgh Medical Center; Aleksandar Rajkovic, MD, PhD, University of California San Francisco

Session Type: Scientific/Education
Topic: Prenatal, Perinatal, and Developmental Genetics
Track: Clinical Research
Audience: Clinicians

Diagnostic genetic testing is a common practice from conception to birth, used to identify couples at risk, embryos with genomic abnormalities, the causes of fetal structural anomalies, pregnancy loss, stillbirth, and neonatal death. A definite molecular diagnosis can provide important information on recurrence risk and reproductive planning. Recent advancements in genomic technologies such as genome/exome sequencing and Optical Genome Mapping have significantly advanced our understanding of the human genome and its role in early fetal development. However, our understanding of genes and variants involved in various reproductive pathologies remains limited. This session brings together clinicians and researchers from around the world with expertise in reproductive medicine, genomic technologies, and machine learning. They will present recent findings from multi-center genomic studies on samples from recurrent pregnancy loss, neonatal death, and pregnancies with ultrasound anomalies, providing new insights into expanded fetal phenotypes for Mendelian conditions, phenotypic variability, parental mosaicism, and sexual dimorphism. The session will also cover novel genes and molecular pathways associated with fetal lethality and adverse reproductive outcomes, as well as the current limitations of translating genetic discoveries into clinical practice for diverse populations. The speakers will discuss cost-effective and technologically improved prenatal options and the potential for precision medicine in perinatology. The session will showcase the diversity of approaches in prenatal diagnosis and highlight the needs and challenges of integrating knowledge from multiple domains. The talks will be followed by a 30-minute panel discussion with all speakers and audience participation.

Speakers:

Genomics of recurrent pregnancy loss: Contribution of known and novel lethal human genes. Christina Tise, MD/PhD, Stanford University

Maximizing diagnostic yield of genomic autopsies in pregnancy loss and perinatal death. Hamish Scott, PhD, SA Pathology

Optical genome mapping: A new option for prenatal diagnosis. Brynn Levy, PhD, Columbia University

Integrated database for genes and conditions associated with pregnancy loss and perinatal death. Marina Sirota, PhD, University of California San Francisco

Friday, November 3, 8:30 – 10:00 am

RNA and nuclear structure: Perspective from the 4D nucleome program
Moderators: Christine Disteche, PhD, University of Washington; Xinxian Deng, PhD, University of Washington

Session Type: Scientific/Education
Topic: Epigenetics
Track: Basic or Translational Research
Audience: Researchers

In this session, attendants will hear from investigators sponsored by the NIH 4DN program. At the start of the session, the moderator will present a short introduction to the 4DN, a highly successful program whose goal is to determine the three-dimensional organization of the nucleus in space and time (the 4th dimension). See also session Rationale. RNA has been nicknamed the dark matter of the nucleus. Indeed, it is only recently that the many roles of the various RNAs found in the nucleus have started to be explored. Yet, there is strong evidence that multiple types of RNAs, including ncRNAs, eRNAs, and mRNAs, can profoundly influence chromatin structure and function throughout development, aging, and disease. Unlike genomic DNA, RNA often has a flexible structure enabling interactions with proteins and DNA, and it can easily travel through the nucleus to perform various tasks to control gene expression and function. RNA can also be epi-modified by m6A RNA methylation, which impacts many processes, including transcription. Well-known examples of lncRNAs that impact chromatin structure and gene expression are XIST that induces silencing and condensation of the X chromosome; TERRA, a repeat containing lncRNA that helps telomere condensation and function via phase formation; and MALAT, shown to be important for the formation of active nuclear speckles essential for splicing. The session is designed to broaden our understanding of nuclear organization by discussing novel reciprocal effects of RNA on chromatin looping and domain boundaries, demonstrating the roles of RNA epigenetic modifications in chromatin folding and gene expression, revealing phase separation of RNA-protein complexes to maintain telomeres, and looking at RNA travels and interactions with nuclear organelles. Coordinated sequencing approaches and live-cell imaging techniques will be presented to show how to map the distribution of various RNAs and their modifications on chromatin and to track RNA molecules within the nucleus. The many interactions of RNAs with gene loci and the spatial distribution of RNAs in the nucleus are critical for normal gene expression and cell function. Specific inherited and acquired diseases such as cancer and viral infection are associated with abnormal nuclear structure. Thus, it is important to better understand the regulatory role of various types of RNAs during cell differentiation and in relation to cell type-specific functions.

Speakers:

Genome-wide analysis of the interplay between chromatin-associated RNA and chromatin architecture in human cells. Sheng Zhong, PhD, University of California San Diego

Enhancer RNA m6A methylation in gene transcription control. Wenbo Li, PhD, University of Texas Health Science Center at Houston

The lncRNA TERRA regulates telomere maintenance in cancer cells via phase separation and condensate formation. Huaiying Zhang, PhD, Carnegie Mellon University

Subnuclear pathways of mRNA travels within the nucleus. Yaron Shav-Tal, PhD, Bar-Ilan University

Saturday, November 4, 8:30 – 10:00 am

Wrestling with social and behavioral genomics: Risks, potential benefits, and ethical responsibility
Moderators: Michelle Meyer, PhD, Geisinger; Erik Parens, PhD, The Hastings Center

Session Type: Ethical, Legal, and Social Issues
Topic: Genetic Counseling, ELSI, Education, and Health Services Research
Track: Ethical, Legal, and Social Issues
Audience: Researchers

Researchers now use genetics to investigate, and create polygenic scores (PGSs) for, social and behavioral phenotypes from obesity to educational attainment. PGSs could be used in research to control for genetic influences, making it easier to learn the effects of environments. PGSs could also be used to direct scarce health, educational, or other resources to people whose PGSs, combined with other biomedical and environmental predictors, suggest they are most in need. But PGSs, which have been disproportionately developed with those of European genetic ancestries, have limited applicability to—and thus limited benefits for—others. In addition to their potential for exacerbating inequities, PGSs also could detract attention from social determinants of health, education, and other important outcomes. And using genetics to explain social and behavioral attributes has an ugly history and is appropriated by those who claim social and economic inequality is natural and unalterable. Session participants are members of a Working Group of diverse academic experts who engaged in sometimes-difficult conversation for three years about the risks and potential benefits of this research and how to conduct and communicate it in ways that minimize its harms and maximize its benefits. In this session, the moderators will first summarize the Working Group's recommendations about genomics research that concerns "sensitive phenotypes" and that compares groups according to such a phenotype. Then the four speakers—two who conduct social and behavioral genomics research and two who have concerns about it—will: describe the potential benefits to health and social science research of incorporating genomics into the study of social and behavioral phenotypes and of the risks of failing to do so; address the risk that genetic research is misinterpreted as demonstrating that human beings can be naturally divided into biologically distinct races; and argue for the importance of engaging relevant communities and responsibly communicating the research. In order to maximize engagement with the audience, each speaker will have 5 minutes and no more than 2 slides in which to present these formal remarks. The moderators will then facilitate 30 minutes of dialogue among the speakers, drawing out points of agreement and disagreement and what they learned from three years of talking with, instead of past, one another. The session will conclude with 30 minutes of audience Q&A.

Speakers:

The ethical and social issues of excavating human differences in social and behavioral genomics. Sandra Lee, PhD, Columbia University

Considering genetic differences in the study of social and behavioral phenotypes. Kathryn Harden, PhD, University of Texas at Austin

Aspirations and limitations to advancing social science through genomics research. Patrick Turley, PhD, University of Southern California

Engaging the public on the risks, potential benefits, and ethical responsibilities of social and behavioral genomics. Daphne Martschenko, PhD, Stanford University

Saturday, November 4, 8:30 – 10:00 am

Equitable access to genomics research: Australian Aboriginal leadership, expertise, and experience
Moderators: Gregory Pratt, BSc, QIMR Berghofer Medical Research Institute; Sarah Medland, PhD, QIMR Berghofer Medical Research Institute

Session Type: Diversity, Equity & Inclusion
Topic: Genetic, Genomic, and Epigenomic Resources and Databases
Track: Diversity, Equity, and Inclusion
Audience: Researchers

This session will share the expertise of Aboriginal researchers of Australia in the genomics space, their diverse and collective wisdom and as members of a National Indigenous Genomics Network (NIGN) of Australia. Individual panelists will describe methods used and results arising from work across the research, policy, and health care spaces. Panelists will share insights about the conduct of ethically, socially responsible, co-designed research that aligns with best practice in the collection, control, use and reporting of biological samples and genomic data of Aboriginal Australians. Key findings and recommendations in the Australian Aboriginal context have generalizability and validity for an international audience with respect to First Nations peoples globally as well as among ancestrally diverse communities; realizing the promise of shared benefit and equitable access to research for real-world impact and in alignment with the principles of data sovereignty and self-determination. Topics covered include community engagement and governance; genetic techniques (limitations, implications, application, and potential); health promotion and literacy; improving access to culturally-competent, high quality genetic health care; workforce development (research, community, and health service sectors), and systems, governance, and policy (a strategic intent). In addition to individual presentations, a moderated panel discussion avails the opportunity for participants to provide feedback to and ask questions of the panel. Attendees are encouraged to participate in a dynamic conversation that explores the significance and importance of sensitive and inclusive processes that ensure socially, ethically, and legally responsible practice. We recognize the responsibility of research to realize the right of all people and peoples to participate in and equitably access research that informs evidence-based genetic health care.

Speakers:

Building national responses to engage and empower Indigenous Australians in precision medicine. Alex Brown, PhD, Australian National University

Empowering Aboriginal and Torres Strait Islander communities in genomics. Azure Hermes, Australian National University

Developing Indigenous data governance in the Australian genomics landscape. Kalinda Griffiths, PhD, UNSW

Integrated genomic healthcare. Gregory Pratt, BSc, QIMR Berghofer Medical Research Institute

Saturday, November 4, 8:30 – 10:00 am

Harnessing return of value: Progress in returning genomic results to individuals in diverse, large-scale programs
Moderators: Joshua Denny, MD, National Institutes of Health; Amy Sturm, MS, 23andMe

Session Type: Scientific/Education
Topic: Genetic, Genomic, and Epigenomic Resources and Databases
Track: Basic or Translational Research; Diversity, Equity, and Inclusion
Audience: Researchers

This panel will describe large-scale efforts to responsibly return genomic results to individuals in diverse, large-scale population genomics programs, focusing on lessons learned from this bidirectional relationship. We will illustrate the importance of elevating participant voices and efforts to improve diversity in genomic studies, navigate regulatory frameworks, and scale return of results operations from thousands to millions. Programs include the All of Us Research Program, 23andMe, Genomics England, and Million Veteran Program: The All of Us Research Program from the National Institutes of Health (NIH) is gathering data from 1 million or more people in the US to accelerate research and improve health. The program focuses on engaging communities historically underrepresented in biomedical research. Since national launch in 2018, >605,000 participants have enrolled. Diverse participant partners (about 80% from underrepresented backgrounds) are sharing health-related data and biospecimens. 23andMe will discuss the direct-to-consumer approach to communicating genomic results directly to >13 million individuals, including FDA-authorized genetic health risk reports. Recent efforts are focused on increasing access in diverse and underrepresented populations, and will highlight approaches leveraged to ensure programs are informed by community needs. Genomics England is sequencing 100,000 genomes from ~85,000 National Health Service patients affected by rare disease or cancer. Recruitment completed in December 2018; research and analysis is ongoing. Programs investigate: sequencing 100,000 newborns, long-read sequencing and multimodal approaches to cancer profiling, and diversity genomics to improve healthcare for non-European ancestry patients, including WGS of 15,000-25,000 participants. The Million Veteran Program at the Veterans Health Administration is a national research program to learn how genes, lifestyle, and military exposures affect health and illness. Since launching in 2011, >925,000 Veterans have joined one of the world's largest programs on genetics and health.

Speakers:
Delivering on the promise to participants: DNA results for All of Us. Alicia Zhou, PhD, Color
Returning genomic results to consumers: The DTC approach. Noura Abul-Husn, MD, PhD, 23andMe
Developing the use of whole genome sequence for rare disease healthcare: The Genomics England experience. Matthew Brown, MD, Genomics England
Pilot return of genetic results to Million Veteran Program participants: Opportunities and challenges. Sumitra Muralidhar, PhD, Dept Veterans Affairs

Saturday, November 4, 8:30 – 10:00 am

Deploying hundreds of mammalian genomes to understand human disease

Moderators: Steven Reilly, PhD, Yale University; Jordan Eizenga, PhD, University of California Santa Cruz

Session Type: Scientific/Education
Topic: Evolutionary and Population Genetics
Track: Basic or Translational Research
Audience: Researchers

Hundreds of thousands of genetic variants are associated with human traits and diseases. However, pinpointing which variants alter molecular function and affect disease risk is an unsolved problem, limiting clinical and biological interpretation of such studies. Evolutionary constraint scores have been used extensively to prioritize candidate variants for further investigation. Such tests measure whether a genomic position has fewer or more mutations over roughly 100 million years of mammalian evolution than expected by chance, with high constraint (fewer mutations) indicative of biological function. Constraint tests have emerged as one of a few tools to predict impacts in non-coding variants, where codes linking sequence to function are limited. This session will discuss recent expansions of evolutionary datasets, development of novel methods to apply constraint estimates, and advances towards understanding the genetic basis of human disease and complex traits. Notably, recent mammalian constraint scores, phyloP, have substantially improved our understanding of which variants are functionally important, thereby accelerating the translation of genomic discoveries into biological knowledge required to understand and treat human disease. The session will start with an investigation into how evolutionary constraint shapes the regulatory grammar of human genomes and present new models to better predict the phenotypic consequence of sequence changes. Speakers will present new evidence showcasing how evolution is a critical lens to understand functional genetic changes underlying disease relevant to human-specific traits such as our advanced cognition and development. The application of advanced machine-learning models to interpret this new large-scale evolutionary data and link genetic changes to phenotypes will be specifically investigated for psychiatric diseases. Speakers will highlight new discoveries across diverse diseases from applying such scores to large databases such as gnomAD. The session will culminate in a panel discussion exploring new possibilities unlocked by having accurate estimates of mammalian constraint at single base pair resolution.

Speakers:

Evolution and disease associations of enhancers that regulate neural plasticity. Katherine Pollard, PhD, Gladstone Institutes/UCSF

Relating enhancer genetic variation across mammals to complex phenotypes using machine learning. Alyssa Lawler, PhD, Broad Institute of MIT and Harvard

Global patterns of genome diversity across the primate radiation. Jeffrey Rogers, PhD, Baylor College of Medicine

Leveraging mammalian and primate constraint to understand genetic variation and human disease. Steven Gazal, PhD, University of Southern California

Saturday, November 4, 8:30 – 10:00 am

Male infertility – Mendelian traits with lifetime implications

Moderators: Donald F. Conrad, PhD, Oregon National Primate Research Center/Oregon Health & Science University; Manon Oud, PhD, Radboudumc

Session Type: Scientific/Education
Topic: Mendelian Phenotypes
Track: Basic or Translational Research
Audience: Researchers

Infertility affects 10-15% of couples and is linked to a variety of etiologies with broad clinical and social consequences. Today, half of infertility cases remain unexplained. Although genetic factors are considered as one of the main causes of infertility, the current clinical workup includes only limited genetic tests (e.g. karyotyping) and the field is far behind other medical specialties in research and in introducing genomic medicine to clinical practice. Uncovering the diversity of genetic forms of infertility is important for the optimal patient management, assessment of potential comorbidities and developing new treatment tools. Recently, joint efforts of the reproductive genetics community have rapidly advanced the knowledge of male infertility, uncovering a broad spectrum of genes implicated in spermatogenesis. These genes span the genome, affecting different stages of sperm production and overall testicular health. Epidemiological studies have shown that >50% of men presenting spermatogenic failure suffer from one or more chronic diseases or major general health conditions. This session will discuss discoveries of novel etiologies of isolated and syndromic monogenic forms spermatogenic failure, their pleiotropy with cancer and other congenital conditions. The talks will also focus on translation of the research outcomes to the clinical practice for the patient benefit in improved counselling and reproductive decision making, as well as assessment and management of genetic comorbidities of infertility. The hallmarks of aging sperm will be discussed in the context of reproductive and general health, such as changes in DNA integrity and methylation patterns and increased telomere length.

Speakers:

Towards clinical exomes in molecular diagnostics of male factor infertility: The national experience in Estonia. Maris Laan, PhD, University of Tartu

Exploring the role of genome instability in male subfertility. Jason Kunisaki, BA, University of Utah

Molecular changes to the human testis during healthy ageing. Sandra Laurentino, PhD, University of Münster

Face, fragrance, and fertility: Insights into developmental pleiotropy learnt from humans with Kallmann Syndrome. Ravikumar Balasubramanian, MBBS, Massachusetts General Hospital/Harvard Medical School

Saturday, November 4, 8:30 – 10:00 am

AI and machine learning in Alzheimer's disease genetics and genomics

Moderators: Degui Zhi, PhD, University of Texas Health Science Center at Houston; Jielin Xu, PhD, Cleveland Clinic

Session Type: Scientific/Education
Topic: Genetic, Genomic, and Epigenomic Resources and Databases
Track: Basic or Translational Research
Audience: Researchers

This session will explore the use of cutting-edge Artificial Intelligence (AI), Machine Learning (ML), and Deep Learning (DL) techniques in the identification of genetic mutations and variants associated with the development of Alzheimer's disease (AD) and related dementias (ADRD). Advancing AD research is a national priority, and current efforts are producing a large amount of data. However, traditional methods are not sufficient to handle the big data analytical challenge. The session will begin with a short introduction from the proposer, followed by four 15-minute talks on diverse topics related to AI/ML in AD research. The first two talks will provide an overview of the ongoing work of the AI4AD Consortium, an 11-site NIA-funded project that uses AI and machine learning to advance AD research, and a deeper dive into a novel framework for drug repositioning using network-based genetic subtyping and graph or clustering-based target and drug prioritization. The third talk will focus on a new brain imaging endophenotype discovery method powered by deep learning. The last talk will feature an AI/ML investigation into the widespread transposable element dysregulation in human brains with AD. The session will conclude with a panel discussion.

Speakers:

Merging worldwide neuroimaging and genomics using AI and machine learning. Paul Thompson, PhD, University of Southern California

Network-based genetic subtyping and drug repositioning for Alzheimer’s disease. Gyungah Jun, PhD, Boston University

Brain imaging endophenotypes for GWAS by unsupervised deep learning. Ziqian Xie, PhD, University of Texas Health Science Center at Houston

Widespread transposable element dysregulation in human brains with Alzheimer’s disease. Yayan Feng, Cleveland Clinic

Saturday, November 4, 8:30 – 10:00 am

Multiplexed assays of variant effect (MAVE): Generating, evaluating, and exploiting for improved clinical genetic diagnosis

Moderators: Frederick Roth, PhD, University of Toronto/Sinai Health; Douglas Fowler, PhD, University of Washington

Session Type: Scientific/Education
Topic: Molecular Effects of Genetic Variation
Track: Basic or Translational Research; Clinical Research
Audience: Clinicians

Over the past decade, high-throughput sequencing-based assays, collectively termed multiplex assays of variant effect (MAVEs), have been developed to systematically characterize a wide array of variant effects on molecular and cellular functions. Unlike previous approaches, MAVEs enable the characterization of many DNA variants within a single, pooled experiment, offering a dramatic advantage in scale. MAVEs present a useful opportunity to incorporate new, highly informative data into variant interpretation during clinical germline genetic testing. However, only a handful of these datasets are routinely used in clinical variant interpretation. As an increasing number of these datasets are generated, a deeper understanding of how they are generated, evaluated and incorporated into clinical testing will be beneficial to clinical practitioners and both translation- and technology-driven researchers. In this session, the speakers will (1) review how MAVEs are designed and evaluated, including their limitations, (2) explain the rigorous steps necessary for the incorporation of MAVEs into clinical variant interpretation workflows, (3) explore recent advances in MAVE technology to expand MAVEs to genes associated with inherited disease, (4) and explore how MAVEs can result in fundamental discovery.

Speakers:

A brief primer on multiplex assays of variant effect (MAVEs) with application to long QT syndrome variants. Ayesha Muhammad, PhD, Vanderbilt University

MAVEs to systematically understand and predict amyloid formation in human disease. Benedetta Bolognesi, PhD, Institute for Bioengineering of Catalonia

Bringing multiplex assays of variant effect (MAVE) data into clinical variant interpretation. Jason Reuter, PhD, Invitae

Multiplex measurement of variant effects in secreted proteins using coagulation factor IX and its role in Hemophilia B as a model. Jill Johnsen, MD, University of Washington