NATIONAL ACADEMIES Sciences Engineering Medicine

Committee on National Statistics

Workshop on Considerations for Returning Individual Genomic Results from Population-Based Surveys: Focus on the National Health and Nutrition Examination Survey

December 2, 7, & 8, 2022

AGENDA

Population surveys collect information from participants by asking questions. Today, many surveys also collect biologic specimens that can be used to analyze a respondent's DNA and other biomarkers. The National Health and Nutrition Examination Survey (NHANES) administers a physical examination, collects biospecimens, and reports some test results (e.g., cholesterol levels) to the participant. Traditionally, NHANES participants have been told that they will not be contacted with personal genetic results. However, clinical science is evolving to encourage more return of individual research results. Therefore, NHANES will revisit the issue of if, when, and how to return genetic results to study participants.

This workshop is being sponsored by the Centers for Disease Control and Prevention (CDC).

Meeting materials and recordings will be available via the Project Website on NationalAcademies.org, Keyword= "Returning Individual Genomic Results"

DAY 1: Friday, December 2, 2022

10:00 – 10:20 am ET

Welcome and Goals for Workshop

- *Brian Harris-Kojetin*, Director, Committee on National Statistics, National Academies of Science, Engineering, & Medicine
- *Brian C. Moyer*, Director, National Center for Health Statistics, Centers for Disease Control and Prevention (CDC)
- *Jeffrey R. Botkin*, Chair, Workshop Planning Committee, University of Utah

10:20 – 11:45 am ET	**I. NHANES: Current Structure and Opportunities for Adding Genomics**
10:20 – 10:35 am	Overview of the NHANES resource ➢ *Alan Simon*, National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC)
10:35 – 10:50 am	NHANES Biospecimen Program ➢ *Alan Simon*, NCHS, CDC
10:50 – 11:05 am	Types of research supported by the current survey data ➢ *Dana Crawford*, Case Western Reserve University (Member, Workshop Planning Committee)
11:05 – 11:20 am	Genetics 101/201: Understanding the current genetic testing landscape ➢ *Ingrid A. Holm*, Boston Children's Hospital (Member, Workshop Planning Committee)
11:20 – 11:45 am	Moderator/discussant questions and reflections ➢ *Leslie G. Biesecker*, National Human Genome Research Institute (NHGRI), National Institutes of Health (NIH) (Member, Workshop Planning Committee)
11:45 am – 12:00 pm ET	**BREAK**
12:00 – 2:00 pm ET	**II. Return of Clinically Actionable Genetic Results**
12:00 – 12:20 pm	What data is being generated? Implications for returning results ➢ *Matt Lebo,* Mass General Brigham
12:20 – 12:40 pm	Ethical arguments regarding the return of research results ➢ *Yvonne Bombard*, University of Toronto
12:40 – 1:00 pm	Current ACMG list, process, and alternatives ➢ *Marc S. Williams*, Geisinger
1:00 – 1:20 pm	Attitudes and outcomes of returning results to participants ➢ *Julie C. Sapp*, NHGRI
1:20 – 1:40 pm	Issues regarding data reanalysis for actionable variants ➢ *Natasha Strande*, Geisinger
1:40 – 2:00 pm	Moderator/discussant questions and reflections ➢ *Jeffrey R. Botkin*, University of Utah (Chair, Workshop Planning Committee)

2:00 – 2:15 pm ET	**BREAK**
2:15 – 3:30 pm ET	**III. Regulatory Issues in the Return of Genetic Results**
2:15 – 2:30 pm	CLIA lab certification and CLIA test validation ➢ *Benjamin Solomon,* National Institutes of Health (NIH)
2:30 – 2:45 pm	Potential FDA oversight and approval ➢ *Beth Collins*, All of Us Research Program, NIH
2:45 – 3:00 pm	Navigating Federal and State-specific Laws Governing Genetic Testing and the Return of Results ➢ *Katherine Blizinsky*, All of Us Research Program, NIH
3:00 – 3:30 pm	Moderator/discussant questions and reflections ➢ *Ingrid A. Holm*, Boston Children's Hospital (Member, Workshop Planning Committee)
3:30 – 4:00 pm ET	**General Discussion (30 mins)**
4:00 pm ET	**Adjournment**
4:00 – 4:30 pm ET	**Planning Committee Discussion (Closed Session)**

DAY 2: Wednesday, December 7, 2022

12:00 – 2:00 pm ET	**IV. Process for the Return of Genetic Results**
12:00 – 12:20 pm	Infrastructure, expertise and other necessary resources to communicate results in a research setting ➢ *Anastasia Wise,* All of Us Research Program, NIH
12:20 – 12:40 pm	Communication strategies in a clinical research setting ➢ *Kathleen A. Leppig*, eMERGE, Kaiser Permanente of Washington
12:40 – 1:00 pm	Communication strategies in a direct-to-consumer context ➢ *Amy Sturm,* 23andMe
1:00 – 1:20 pm	Special issues for returns to participants in low-resource communities: Lessons from the Healthy Nevada Project ➢ *Joe Grzymski & Gai Elhanan*, Healthy Nevada Project
1:20 – 1:40 pm	Special issues for returns to participants in low-resource communities: Lessons from the Bio*Me* project ➢ *Noura Abul-Husn*, Icahn School of Medicine at Mount Sinai
1:40 – 2:00 pm	Moderator/discussant questions and reflections ➢ *Adam Buchanan*, Geisinger (Member, Workshop Planning Committee)
2:00 – 2:15 pm ET	**BREAK**
2:15 – 3:30 pm ET	**V. Informed Consent When Considering Returning Genetic Results to Survey Participants**
2:15 – 2:30 pm	Community Engagement and Informed Consent in NHANES ➢ *Duong (Tony) Nguyen,* CDC
2:30 – 2:50 pm	Informed consent content for return of research results and biobanking ➢ *David Magnus*, Stanford University
2:50 – 3:10 pm	The informed consent process for return of results and biobanking ➢ *Michelle N. Meyer*, Geisinger
3:10 – 4:00 pm	Moderator/discussant questions and reflections ➢ *Amy McGuire*, Baylor College of Medicine
3:30 – 4:00 pm ET	**General Discussion (30 mins)**
4:00 ET	**Adjournment**

DAY 3: Thursday, December 8, 2022

1:00 – 1:10 pm ET — **Recap of the Discussion Thus Far**

- *Jeffrey R. Botkin*, University of Utah (Chair, Workshop Planning Committee)

1:10 – 3:00 pm ET — **VI. Considerations in the Return of Genetic Results: Lessons from Other Research Studies**

1:10 – 1:30 pm — Genomics England

- *David Bick,* Genomics England

1:30 – 1:50 pm — Million Veteran Program

- *Jason Vassy*, Harvard Medical School

1:50 – 2:10 pm — Alabama Genomic Health Initiative

- *Bruce Korf*, University of Alabama at Birmingham

2:10 – 2:30 pm — All of Us

- *Stephanie Devaney,* All of Us Research Program, NIH

2:30 – 3:00 pm — Moderator/discussant questions and reflections

- *Leslie G. Biesecker*, NHGRI, NIH (Member, Workshop Planning Committee)

3:00 – 3:15 pm ET — **BREAK**

3:15 – 4:15 pm ET — **Panel Discussion: Key Themes and Considerations for Future NHANES**

- *Jeffrey R. Botkin*, University of Utah (Chair, Workshop Planning Committee)
- Workshop Planning Committee Members:
  - *Leslie G. Biesecker*, NHGRI, NIH
  - *Natasha Bonhomme,* Expecting Health
  - *Adam Buchanan*, Geisinger
  - *Dana Crawford,* Case Western Reserve University
  - *Ingrid A. Holm*, Boston Children's Hospital
  - *David Forster,* Western Institutional Review Board-Copernicus Group (WCG)

4:15 pm ET — **Adjournment**

Genomics NHANES NCHS December 2022 Workshop Bios

PLANNING COMMITTEE

Jeffrey R. Botkin (Chair)

Dr. Jeffrey R. Botkin, MD, MPH is an Emeritus Professor of Pediatrics and was an Adjunct Professor of Human Genetics and Internal Medicine at the University of Utah. He is the past Chief of the Division of Medical Ethics and Humanities and served for 17 years as the Associate Vice President for Research Integrity. Dr. Botkin chaired the HHS Advisory Committee on Human Research Protections and was a member of the Secretary's Advisory Committee on Heritable Diseases in Newborns. He serves on the FDA Pediatric Ethics Subcommittee and chairs the NIH's Embryonic Stem Cell Eligibility Working Group. He is a graduate of Princeton University and received an MD from the University of Pittsburgh, and an MPH from Johns Hopkins University. He received consistent NIH funding for research on the ethical, legal, and social implications of genetic technologies with a particular emphasis on research ethics, biobanking, newborn screening, and prenatal diagnosis. Dr. Botkin served on the planning committee for the 2014 National Academies of Science, Engineering and Medicine's Workshop on "Guidelines for Returning Individual Results for Genome Research Using Population-based Banked Specimens" and chaired the 2018 consensus committee which produced a publication titled "Returning Individual Research Results to Participants: Guidance for a New Research Paradigm."

Leslie G. Biesecker

Dr. Leslie G. Biesecker, MD is a Distinguished Investigator, and Director of the Center for Precision Health Research at the National Human Genome Research Institute of the National Institutes of Health, which he joined in 1993. He uses genetic and genomic technologies to study the etiology of genetic disorders and has published over 300 primary research articles, reviews, and chapters and developed the ClinSeq® program, which began clinical genomics research in 2006, before the widespread availability of next generation sequencing. He is double board certified in Pediatrics and Medical Genetics. He was elected to the National Academy of Medicine of the National Academy of Science in 2018 and was the President of the American Society of Human Genetics for 2019.

Natasha Bonhomme

Ms. Natasha Bonhomme is the founder of Expecting Health, an organization born from Genetic Alliance that is dedicated specifically on sharing science-based and policy-informed information that reflects the lived experiences of individuals and their families. A direct product of her role as Chief Strategy Officer at Genetic Alliance where she has overseen Genetic Alliance's maternal and child health initiatives, Expecting Health accomplishes their mission by bringing a range of consumer and professional stakeholders together to address the need for clear, science-based information for families and individuals through tangible, actionable messages. As Director of Baby's First Test, Natasha has testified before the US Senate Health, Education, Labor and Pension Committee's Subcommittee on Children and Families on the importance of public education for newborn screening. Natasha serves on a range of committees including: Co-Chair of the Genetics and Bioethics Committee, American Public Health Association; the Association of Public Health Laboratories Committee on Newborn Screening and Genetics in Public Health; and the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. In 2011, she obtained a Certificate from Georgetown University in Non-Profit Executive Management. Ms. Bonhomme is the Co-Chair of the Developing Leaders Program for Planned Parenthood of Metropolitan Washington.

Adam Buchanan

Mr. Adam H. Buchanan, MS, MPH is Associate Professor and Director of the Genomic Medicine Institute at Geisinger. Mr. Buchanan is interim director of Geisinger's MyCode Genomic Screening and Counseling program that screens biobank participants' exomes for clinically actionable findings associated with increased risk for cancer, cardiovascular disease and other conditions. Mr. Buchanan is an NIH-funded investigator and board-certified and licensed genetic counselor with expertise in assessing genetic counseling outcomes and cancer risk management behaviors. He is also a former president of the American Board of Genetic Counseling. His research interests include outcomes of genomic screening, delivery of genetics services, and performance of multi-cancer early detection tests. He has completed training in implementation science from the National Cancer Institute. Mr. Buchanan

received a master's in public health, with focus in health behavior science from the University of North Carolina – Chapel Hill, and a master's in science in genetic counseling from the University of North Carolina – Greensboro.

Dana C. Crawford

Dr. Dana C. Crawford, PhD, is Professor of Population and Quantitative Health Sciences at Case Western Reserve University (CWRU) and Associate Director for Population and Diversity Research in the CWRU Cleveland Institute for Computational Biology. Dr. Crawford also holds a secondary appointment in CWRU's Department of Genetics and Genome Sciences. Dr. Crawford's expertise is in genetic epidemiology and human genetics, and her current research interests map to the interface of genetic epidemiology and big data biomedical informatics. Her laboratory accesses epidemiologic and clinical collections to characterize common and rare genetic variants associated with human diseases in diverse populations. She also has an interest in identifying pleiotropy and environmental modifiers of these genetic associations, including pharmacogenomics. Dr. Crawford is a three-time Kavli Frontiers in Science Fellow (2012, 2013, and 2014), and in 2020, she was elected as a Fellow of the American Association for the Advancement of Science (AAAS) in Biological Sciences for "distinguished contributions in pioneering phenome-wide association studies and in developing and leading genetic studies in under-represented minority populations." Dr. Crawford earned her BS from Vanderbilt University and a PhD from Emory University in the Genetics and Molecular Biology Program.

David Forster

Mr. David G. Forster joined Western IRB (WIRB) in 1996 and is currently the Chief Compliance Officer and Chief Privacy Officer for the Western Institutional Review Board-Copernicus Group (WCG). Mr. Forster co-chairs the Secretary's Advisory Committee on Human Research Protections (SACHRP) Sub-Committee on Harmonization (SOH). He previously served a four-year term as a member of SACHRP, and was a member of the SACHRP Sub-Committee on Inclusion of Individuals with Impaired Decision-Making in Research (SIIIDR). Mr. Forster also served on the Certified IRB Professional (CIP) Council. In his role on the SACHRP subcommittee, Mr. Forster worked on drafting SACHRP's five recommendations regarding the return of research results to research subjects. Mr. Forster also provided input on the All of Us study consent form during its development. He has expertise in bioethics, laws and regulations governing the protection of human subjects in research, and privacy. Mr. Forster has a J.D. and a Masters in Medical Ethics from the University of Washington.

Ingrid A. Holm

Dr. Ingrid A. Holm, MD, MPH is Professor of Pediatrics at Harvard Medical School (HMS), faculty in the Division of Genetics and Genomics and the Division of Endocrinology at Boston Children's Hospital (BCH), and faculty at the HMS Center for Bioethics. She is Associate Director of Robert's Program for Sudden Unexpected Death in Pediatrics (SUDP) Program where she leads studies to identify genetic contributions to SUDP, and she is a member of the Harvard Undiagnosed Disease Network (UDN) site. She is also co-PI with Dr. Robert Green of the "BabySeq2" project National Center for Advancing Translational Sciences-funded U01. She was co-investigator of the BCH/Brigham and Women's Hospital (BWH) U19 "BabySeq" project. Since 2012, she has been a member of the NHGRI-funded Electronic Medical Records and Genomics (eMERGE) Network. Dr. Holm conducts empirical, mixed-methods research to study the impact of returning genomic information. She is a pediatric geneticist with clinical focus on bone diseases and disorders of sex development. Her other interest is in rare disease research. She completed her pediatric residency and dual fellowship in Medical Genetics and Pediatric Endocrinology at BCH, and the Harvard Pediatric Health Services Research Fellowship and a MPH at the Harvard School of Public Health.

PRESENTERS

Noura Abul-husn

Noura Abul-Husn, PhD, MD, is the Vice President of Genomic Health at 23andMe and Associate Professor of Medicine at the Icahn School of Medicine at Mount Sinai. She is a principal investigator in the eMERGE Network, which is integrating polygenic risk scores into clinical care. She recently joined 23andMe as Vice President of Genomic Health, to develop strategies for genome-informed disease prevention and management. Noura's scientific contributions include pioneering genome-first approaches in electronic health record-linked biobanks to provide novel clinical insights and inform therapeutic discovery. In her role at Mount Sinai, she launched a genomic screening program tailored to ancestrally diverse biobank participants. She previously served as Director of

Translational Genetics at the Regeneron Genetics Center, during which time she received a 40 under 40 Rising Star Award. She is the recipient of the 2021 Dr. Michael S. Watson Genetic & Genomic Medicine Innovation Award from the ACMG Foundation for Genetic and Genomic Medicine. Noura completed her MD, PhD, and residency at Mount Sinai in New York, and was elected to the Alpha Omega Alpha Medical Honor Society. She is board-certified in Internal Medicine and Medical Genetics.

David Bick

David Bick, MD, is the Principal Clinician for the Newborn Genomes Programme at Genomics England. Prior to his work in England, he was the Chief Medical Officer and a faculty investigator at the HudsonAlpha Institute for Biotechnology. David also served as the Medical Director of the Smith Family Clinic for Genomic Medicine, located on the campus of HudsonAlpha Institute for Biotechnology and the Laboratory Director of the HudsonAlpha Clinical Services Laboratory. He came to HudsonAlpha from the Medical College of Wisconsin where he was Professor in the Department of Pediatrics and the Department of Obstetrics & Gynecology. David is board-certified in Pediatrics, Clinical Genetics, and Clinical Molecular Genetics. His laboratories were the first in the world to offer whole genome sequencing as a clinical test. He also developed the first Genomic Medicine Clinic in the United States. David received his medical degree from George Washington University School of Medicine in 1981 and completed his residency in Pediatrics at Yale-New Haven Hospital in New Haven, CT. At the Yale University School of Medicine, he completed a fellowship in Human Genetics and Pediatrics in 1986, followed by a post-doctoral research fellowship in Human Genetics in 1987.

Katherine Blizinsky

Katherine Blizinsky, PhD, is the Policy Director for the All of Us Research Program, leading program policy activities, including legislative and regulatory policy analysis, and the development and strategic visioning for work regarding ethical, legal, and social implications (ELSI). On Capitol Hill, she worked with the Senate Health, Education, Labor, and Pensions Committee under Ranking Member Patty Murray, where, among other roles, she helped lead the drafting and negotiation of the 21st Century Cures Act. Katherine has policy experience with both the legislative and executive branches. She has drawn on her expertise in the areas of data governance, genomics, and ethical research conduct to her work at All of Us has. A neuroscientist and geneticist specializing in gene-environment interaction, she continues to be involved in academic research and lectures frequently on genomics, neuroscience, legal and regulatory policy, and ELSI.

Yvonne Bombard

Yvonne Bombard, PhD, is a genomics health services researcher and Scientist at the Li Ka Shing Knowledge Institute of St. Michael's Hospital, Unity Health Toronto. She is an Associate Professor at the Institute of Health Policy, Management and Evaluation at the University of Toronto and directs the Genomics Health Services Research Program at St. Michael's Hospital. She holds the Canada Research Chair in Genomics Health Services and Policy. She sets research direction at national and international levels as Board Member of the American Society of Human Genetics and CIHR's Institute of Genetics. Yvonne advises on funding recommendations on emerging genetic testing technologies for Ontario. She was the inaugural recipient of the Maurice McGregor Award for Demonstrated Excellence and Leadership Potential from the Canadian Agency for Drugs and Technologies in Health (CADTH) and received a 'Rising Star' award from CIHR's Institute of Health Services and Policy Research. She has been awarded a CIHR Foundation grant as an Early Career Investigator, CIHR Maud Menten Early Career Prize in Genetics and recently received Canadian Cancer Society's early career investigator award for her work and policy change.

Beth Collins

Beth Collins, M.A., is a contractor for Columbus Technologies and Services. She currently works with the NIH All of Us Research Program to ensure IDE Sponsor communications and essential documentation meet compliance under 21 CFR 812. In her career as a certified clinical research professional and bioethicist, she has worked with over 30 investigator-initiated early-phase studies requiring either an investigational new drug application (IND) or investigational device exemption (IDE) from the FDA and ranging from novel drug combinations (hematological malignancies) to implantable medical devices. Beth Collins is also an interdisciplinary artist and graduate student in Virginia Commonwealth University's MATX doctoral program, performing research at the intersection of arts and medical innovation.

Stephanie Devaney

Stephanie Devaney, PhD, is the Chief Operating Officer of the All of Us Research Program at the National Institutes of Health. In this role, she is responsible for overseeing the operations of the All of Us Research Program to ensure the program fulfills its mission of advancing precision medicine research. Prior to this, she led the coordination of the Precision Medicine Initiative from the Office of the Chief of Staff at the White House. In this role, she coordinated the many components of the Initiative and guided the vision of the overall effort, along with the many federal partners. Before joining the White House, Stephane worked in the Office of the Director at the National Institutes of Health. There she helped advance policies critical to biomedical research and the NIH mission, and assisted in the development of programs and research initiatives to advance national scientific priorities. Stephanie received her PhD in Molecular Genetics from the George Washington University and her B.S. in Biology from The Ohio State University.

Gai Elhanan

Gai Elhanan, MD, is a veteran physician (Internal Medicine and Infectious Diseases), healthcare researcher, and data scientist. He is currently a clinical data research scientist with the Center for Genomic Medicine at the Desert Research Institute (DRI) and the Healthy Nevada Project in Reno, Nevada. He has more than 25 years of experience with healthcare information systems, including research, design, development, and implementation in clinical and administrative environments. He possesses unique knowledge in the field of semantic networks and medical and healthcare ontologies. His formal medical informatics education involved completing a post-doctoral fellowship at the Medical Informatics department of the Presbyterian Medical Center at Columbia University; this provided him with a broad skill set in the informatics field.

Joseph Grzymski

Joseph Grzymski, PhD, is the Chief Scientific Officer of Renown Health, the Director of the Renown Institute for Health Innovation, and a faculty member at the Desert Research Institute (DRI). He conceived of and leads the Healthy Nevada Project. The Healthy Nevada Project (HNP) is a population genetics study that has enrolled, consented, and collected DNA and other health determinants data from more than 50,000 participants throughout Nevada. He is the principal investigator of a genetics study on NASH risk sponsored by Gilead Sciences as well as of an NIH R01 grant focusing on gene and environment interactions. He and his team have helped transform Northern Nevada into a hotspot of population health due to the HNP and an array of high-impact papers. Joseph works closely with a variety of federal agencies on population genomics best practices. He received his PhD from Rutgers University, and was a postdoc at Rockefeller University, a Fulbright Scholar and a Bowdoin College graduate.

Bruce Korf

Bruce Korf, PhD, is Associate Dean for Genomic Medicine and Chief Genomics Officer at University of Alabama at Birmingham and Wayne H. and Sara Crews Finley Endowed Chair in Medical Genetics at the UAB Heersink School of Medicine. He is a medical geneticist who is certified by the American Board of Medical Genetics and Genomics in clinical genetics, clinical cytogenetics, and clinical molecular genetics. He is also certified by the American Board of Pediatrics and the American Board of Psychiatry and Neurology (Child Neurology). He is co-editor of Emery and Rimoin's Principles and Practice of Medical Genetics and editor-in-chief of the American Journal of Human Genetics. His major research interests are the diagnosis and treatment of neurofibromatosis and the integration of genomics into medical practice.

Matthew Lebo

Matthew Lebo, PhD, is the Chief Laboratory Director of the Laboratory for Molecular Medicine (LMM), a CLIA-certified molecular diagnostics laboratory, and as the Director of Bioinformatics within Mass General Brigham Personalized Medicine. He is an Associate Professor of Pathology at Harvard Medical School and an Associate Member of the Broad Institute of MIT and Harvard. Matthew's research focuses on driving forward the routine use of genomics and computational biology in translational and clinical applications, specifically in genomic-based applications and high-throughput screening of unaffected individuals. He also participates in standards and guidelines development, including co-chairing the ClinGen Low-Penetrance/Risk Allele Work Group and being involved in activities with ACMG, AMP, CAP, NSGC, CLSI, and the Medical Genome Initiative.

Kathleen Leppig

Kathleen A. Leppig, MD is Chief of Genetic Services at Kaiser Permanente of Washington and Clinical Professor in the Department of Medical Genetics at the University of Washington. She is a medical geneticist who is certified by the American Board of Medical Genetics and Genomics in clinical genetics and clinical cytogenetics. She is involved in the development of genetic and genomic services for Kaiser Permanente, focusing on how best to provide these services across a large population. She has a 16-year collaboration with Vietnam National Hospital of Pediatrics to support the development of medical genetics care in Vietnam. She is a section editor for *Genetics in Medicine*. She is involved in a number of research projects including a health care system-led familial risk notification project and the Cascade Traceback study for women with a history of ovarian cancer. She is a clinical lead at the Pacific Northwest Site for the Undiagnosed Disease Network.

David Magnus

David Magnus, PhD, is Thomas A. Raffin Professor of Medicine and Biomedical Ethics, and Professor of Pediatrics, Medicine, and by Courtesy of Bioengineering and Associate Dean of Research at Stanford University. He is the Director of the Stanford Center for Biomedical Ethics, a member of the Stanford Hospital and Clinics Ethics Committee, past President of the Association of Bioethics Program Directors, and the Editor-in-Chief of the American Journal of Bioethics. He is currently the Vice-Chair of the IRB for the NIH Precision Medicine Initiative ("All of Us"). He is a member of Stanford's IRB and Stem Cell Research Oversight Committee and has extensive experience as a research ethics consultant. His research focuses on a wide range of topics in bioethics, including research ethics, the ethics of comparative effectiveness research, transplant ethics, genetics/genomics, issues in patient/physician communication and artificial intelligence and machine learning in medicine.

Amy McGuire

Amy McGuire, JD, PhD, is the Leon Jaworski Professor of Biomedical Ethics and Director of the Center for Medical Ethics and Health Policy at Baylor College of Medicine. Currently, she is on the board of the Greenwall Foundation, is a Hasting's Center Fellow, and is a member of the Scientific Advisory Board for Geisinger Research and The Morgridge Institute for Research. She has served as a member of the National Advisory Council for Human Genome Research and as an advisor to the X Prize in Genomics. She researches ethical and policy issues related to emerging technologies and innovative therapeutics, with a particular focus on genetics and genomics, big data, neuropsychology, and the clinical integration of novel neurological devices. Her research is funded by the National Institutes of Health. Amy has received numerous teaching awards at Baylor College of Medicine, was recognized by the Texas Executive Women as a Woman on the Move in 2016, and was invited to give two TED talks in 2014 and 2022.

Michelle N. Meyer

Michelle N. Meyer, JD, PhD, is an Associate Professor and Chair of the Department of Bioethics and Decision Sciences at Geisinger, where she is also Faculty Co-Director of the Behavioral Insights Team in Geisinger's Steele Institute for Health Innovation. In addition to engaging in normative and legal scholarship, she empirically investigates judgments and decision-making in the areas of healthcare, science and innovation using experimental and other methods. For instance, she is completing an NIH-funded RCT comparing standard, in-person consent to Geisinger's MyCode biobank, which includes the return of clinically actionable results to an eConsent co-developed with those who designed the eConsent used by All of Us. Michelle earned a PhD in religious studies, with a focus on applied ethics, from the University of Virginia and a J.D. from Harvard Law School, where she was an editor of the Harvard Law Review. Following law school, she clerked on the U.S. Court of Appeals for the Eleventh Circuit.

Brian C. Moyer

Brian C. Moyer, PhD, is the Director of the U.S. National Center for Health Statistics. As Director, Dr. Moyer provides executive leadership and strategic direction for the Center's statistical programs and policies. He serves as senior advisor to the Centers for Disease Control and Prevention and to the Secretary of the U.S. Department of Health and Human Services; he also serves as the Statistical Official for the Department. Prior to joining NCHS, Dr. Moyer spent more than 25 years with the U.S. Department of Commerce. He served as Director of the Bureau of Economic Analysis (BEA), where he led modernization efforts to improve official economic statistics, including the measures of gross domestic product (GDP). Dr. Moyer received a bachelor's and master's degrees in economics from the University of Maryland and a PhD in economics in 2002 from American University.

Duong (Tony) Nguyen

Duong "Tony" Nguyen, DO, is a pediatrician that has worked as an active-duty Army physician, in private practice, and at the local health department level before returning to federal service as an active-duty Public Health Service Officer. He began his career at the CDC as a member of the Epidemic Intelligence Service (EIS) assigned to the National Health and Nutrition Examination Survey (NHANES). After EIS, he became the NHANES Chief Medical Officer and served as Acting Chief of the Operations Branch. Tony also currently serves as the Human Subjects Contact for NHANES. As Chief Medical Officer, he provides the clinical oversight for health examinations, provides medical input to NHANES planning and operations, and is the medical point of contact for participants or medical providers regarding NHANES test results. He attended medical school at the Lake Erie College of Osteopathic Medicine and completed residency at Walter Reed Army Medical Center.

Julie C. Sapp

Julie C. Sapp, ScM., CGC, works as part of a multi-disciplinary research team at the Center for Precision Health Research at NHGRI, where she draws upon her genetic counseling training and over a decade of behavioral science research experience to promote the integration of genomics into medical practice. The diverse clinical research portfolio of the laboratory and her role as primary clinician working directly with research participants has positioned her to investigate a varied set of important social and behavioral questions related to clinical genomics and genetic counseling. Her work in this area has included qualitative and quantitative investigations of social and behavioral constructs such as the psychosocial impact of genetic disease, patient attitudes and beliefs, decision-making, research ethics, and informed consent. More recently, she has extended her early work to include applying these approaches to understand how best to meet the clinical demands of the expanding role of genome and exome sequencing and how to maximize the utility of genomic findings. Her research focus in these efforts is to investigate the clinical utility of genomic techniques to develop best practices for the return of results and inform future studies of the expanding role of genomics.

Alan Simon

Alan Simon, MD, is the Director of the Division of Health and Nutrition Examination Surveys (DHANES) at the National Center for Health Statistics (NCHS). Prior to this, he was a medical officer/project scientist for the IDeA States Pediatric Clinical Trials Network in the Environmental influences on Child Health Outcomes (ECHO) program, NIH Office of the Director where he focused on clinical trials engaging children in underserved states. Previously, he worked in the U.S. Department of Health and Human Services Office on Women's Health in the Office of the Assistant Secretary for Health, where his work within women and girls' health included sports participation, eating disorders, and opioid misuse. Alan also has a decade of experience as a medical officer in the Office of Analysis and Epidemiology and the Division of Health Care Statistics at NCHS. He has authored over 70 publications in the areas of health, health services, and epidemiology. He received a B.A. in Economics from Cornell University and an MD from Columbia University College of Physicians and Surgeons. He completed his residency in Pediatrics at Children's National Medical Center in Washington, D.C. After his residency, he was a Robert Wood Johnson Clinical Scholar at Johns Hopkins University.

Ben Solomon

Ben Solomon, PhD, is Clinical Director of the National Human Genome Research Unit (NHGRI), part of the National Institutes of Health (NIH); he also leads an NHGRI research group that focuses on the use of artificial intelligence to analyze datasets relevant to genetic conditions. He trained in clinical genetics and pediatrics through a joint NHGRI/Children's National Medical center program. Prior to rejoining NHGRI as Clinical Director in 2019, he served as Chief of the Division of Medical Genomics at the Inova Translational Medicine Institute, and was Managing Director of GeneDx, a clinical and research genetics/genomics sequencing lab. He received his medical degree from Dartmouth.

Natasha Strande

Natasha Strande, PhD, DABMGG, FACMG, Dr. is an Assistant Professor within the department of Genomic Health and Autism and Developmental Medicine Institute at Geisinger and the Clinical Laboratory Director for the MyCode Community Health Initiative. She received her B.S. in Biochemistry from Denison University and continued her scientific training at University of North Carolina at Chapel Hill where she received her PhD in Biochemistry and Biophysics, followed by post-doctoral training in the Department of Genetics. She completed her molecular genetics

and cytogenetics laboratory fellowships at UNC and is board-certified in Laboratory Genetics and Genomics by the American Board of Medical Genetics and Genomics (ABMGG). As Clinical Laboratory Director for Geisinger's Precision Health Program, she oversees the MyCode Biobank and the variant interpretation team that screens exome data generated through the MyCode DiscovEHR collaboration to identify clinically actionable variants for return by the Genomic Screening and Counseling team.

Amy Sturm

Amy Sturm, MS, CGC, is the Director of Population Health Genomics at 23andMe. Before joining 23andMe, Amy was a Professor and genetic counselor in the Geisinger Genomic Medicine Institute for 5 years, where she served as Principal Investigator of the MyCode Community Health Initiative and Director of the MyCode Genomic Screening and Counseling Program. From 2019- 2022, Amy served as Chair of the Advisory Board to the Genetic Counseling Resource for the NIH's All of Us Research Program. During her time at Geisinger, she was also the Principal Investigator of an NIH-funded grant that utilized tools from implementation science to develop patient-centered identification and cascade testing programs for familial hypercholesterolemia. Before her time at Geisinger, Amy was an Associate Professor and genetic counselor in the Division of Human Genetics at The Ohio State University Medical Center. Amy served as the 2019 President of the National Society of Genetic Counselors, and serves on the American Heart Association's Genomic and Precision Medicine leadership council, the MVP-Return of Actionable Results Advisory Committee, and the Scientific Advisory Board of the Family Heart Foundation.

Jason Vassy

Jason Vassy, MD, MPH, is an Associate Professor of Medicine at Harvard Medical School, a clinician-investigator at the Veterans Affairs (VA) Boston Healthcare System and Brigham and Women's Hospital, and a founding member of Precision Population Health at Ariadne Labs. He is a practicing primary care internist and researcher in the implementation and evaluation of genomic medicine interventions. For the last decade, he has directed the Genomes2Veterans Research Program at VA Boston, where his research examines the clinical utility of genetic and genomic testing in various primary care clinical contexts. Current projects include clinical trials of pharmacogenetic testing, polygenic risk scores, and return of unanticipated genetic results among participants of the Million Veteran Program. He is also a principal investigator for the VA All of Us Research Program. He earned his MD degree from Washington University School of Medicine before completing an internal medicine residency at the University of Pennsylvania, as well as a Harvard General Internal Medicine Research Fellowship at Massachusetts General Hospital.

Marc S. Williams

Marc S. Williams, MD, FAAP, FACMG, FACMI, is a clinical geneticist and research scientist. He is professor and director emeritus of Geisinger's Department of Genomic Health. He is on the NHGRI Genomic Medicine working group, and was a member of the Secretary's Advisory Committee for Genetics, Health and Society. He is currently president of the American College of Medical Genetics and Genomics. He is also past chair of the ACMG Committee on the Economics of Genetic Services and founded the ACMG Quality Improvement Special Interest Group. Marc is a member of the Scientific Advisory Boards of the Clinical Pharmacogenetic Implementation Consortium (CPIC), the NIH Undiagnosed Diseases Project, and Online Mendelian Inheritance in Man. He has authored over 200 articles on a variety of topics including the economic evaluation and value of genetic services, implementation of genomic medicine, and the use of informatics to facilitate genomic medicine and precision health.

Anastasia Wise

Anastasia Wise, PhD, is the Director of Scientific Return to Participants and Impact for the All of Us Research Program and leads the responsible return of genomic results to participants. Prior to joining the All of Us Research Program, Anastasia worked at the National Human Genome Research Institute where she served as program director for the NIH Common Fund's Undiagnosed Diseases Network, building a sustainable national resource to diagnose both rare and previously undiagnosed diseases through team science. She also managed the Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) program, exploring the potential implications, challenges and opportunities associated with the possible use of genomic sequence information in the newborn period. Her other research interests include gene-environment interactions in complex disease, pharmaco- and toxicogenomics, and ethical, legal, and social issues related to the use of genetic information. Anastasia received her PhD in genetics and genomics from Duke University, and her B.S. in Environmental Science from the University of North Carolina at Chapel Hill.

Workshop Primer: Background and Context about the National Health and Nutrition Examination Survey (NHANES)

Created by: Workshop planning committee and staff

Document Purpose: To provide key information about the NHANES to inform the 2022 workshop on "Considerations for Returning Individual Genomic Results from Population-Based Surveys: Focus on the NHANES." This document is not intended to be comprehensive. Readers who need additional information are encouraged to visit the NHANES website to find additional information (www.cdc.gov/nchs/nhanes) and/or direct questions via email to the workshop study director, Celeste Stone (cstone@nas.edu).

About the NHANES Data Collection

- The NHANES program began in the early 1960s and is a continuous program that has a changing focus on a variety of health and nutrition measurements to meet emerging needs.
- This survey is cross-sectional and there is no active tracking of participants following their participation in the survey.
- NHANES is a complex sample survey which involves "the identification [of] and data collection [based on] a sample of population units [e.g., individuals, institutions] (SagePub, 2022)." (Also see: CDC, 2020)
- The current survey examines a nationally representative sample of about 5,000 persons each year. These persons are located in counties across the country, 15 of which are visited each year.
- Oversampling of certain population subgroups is also done to increase the reliability and precision of health status indicator estimates for these particular subgroups.
- The NHANES interview includes demographic, socioeconomic, dietary, and health-related questions. The examination component consists of medical, dental, and physiological measurements, as well as laboratory tests administered by highly trained personnel.
- Findings from this survey are used to determine the prevalence of major diseases and risk factors for diseases. Data from this survey are used in epidemiological studies and health sciences research, which help develop sound public health policy, direct and design health programs and services, and expand the health knowledge for the Nation.

Reporting Findings to NHANES Participants

- All survey participants receive a report of findings approximately 12-16 weeks after their participation in the main survey (household interview and to visit mobile examination) and this is generally the last contact NHANES initiates with survey participants.
- NHANES provides health measurement and test results to all participants who have completed at least one component of the health examination.
- Table 1 below provides information about the three levels of findings, including how those findings are communicated with participants.
- For a NHANES test result to be reported, it must be "clinically actionable" for participant and/or medical provider.
- To be clinically actionable or reportable, the test result must either:
  - Inform clinical decision-making *OR* - Inform participants so that precautions and/or changes to health behavior can be made
  - Labs: Historically to be eligible for reporting to participants must be FDA approved and a CLIA-certified test from CLIA-certified laboratory. (Also see "Laboratory Developed tests" in the Workshop Glossary.)
- NCHS has an in-house survey response team available to answer calls from sample participants regarding questions about test results from the Report of Finding System.

Informed Consent

- When NHANES last collected DNA (2011-2012), there was a separate informed consent
  - DNA Specimens were collected in NHANES III, 1999-2002 and 2007-2012. Since 1999 this collection consists of adults only.
  - Consent for Specimen Storage and Continuing Studies for DNA
- NHANES currently has informed consent for 2 separate components (here) as follows:
  - Home interview and Examination Consent
  - Consent/Assent and Parental Permission for Specimen Storage and Continuing Studies (e.g., plasma, sera, and urine)

Biospecimen Program

- Serum, Plasma, and Urine Specimens
- DNA Specimens and Genetic Data Program
- Access
  - Specimens
    - Proposal Process: Including ensuring that research does not generate clinically significant results (i.e., traditionally ACMG for DNA specimens)
  - Resulting data
    - Public use data are available on the NHANES website
    - To guarantee the confidentiality of the survey participants, Limited Access data are available in the NCHS's Research Data Center.
      - This includes Personally Identifiable Information (PII) and genetic data, indirect PII, and other sensitive data.

Glossary of Terms and Acronyms: Background and Context for 2022 Workshop

Created by: Workshop planning committee and staff

Living Document: Last updated 11/28/2022

Project: National Academies for Science, Engineering, and Medicine's CDC-sponsored Workshop on Considerations for Returning Individual Genomic Results from Population-Based Surveys: Focus on the National Health and Nutrition Examination Survey

Document Purpose: Created for internal use to facilitate the work of the group (e.g., staff; sponsors; committee members; speakers; moderators; discussants) across contexts and disciplines. This is a living document that will be updated periodically as needed and requested.

National Health and Nutrition Examination Survey (NHANES) - A program of studies designed to assess the health and nutritional status of adults and children in the United States. The survey is unique in that it combines interviews and physical examinations.

- NHANES is a major program of the National Center for Health Statistics (NCHS).
- NCHS is part of the Centers for Disease Control and Prevention (CDC) and has the responsibility for producing vital and health statistics for the Nation.

Survey - In the NHANES context and more generally in the social science, behavioral, and population studies research space the word "surveys" is often used to refer to "the identification [of] and data collection [based on] a sample of population units [e.g., individuals, institutions] (SagePub, 2022)." These are often data collection programs which include a traditional "survey" (e.g., a questionnaire that a respondent fills out) and other forms of data collection including but not limited to records linkage consent, biological data collection, environmental data collection (e.g., soil samples), and other means of data collection.

- Therefore, in the NHANES context, the term "survey" refers to the entire set of data collected, including questionnaires/forms, physical examination results, and biospecimens (including plasma, serum, urine)."

Active Survey - In the context of this workshop, "active survey" refers to data from the primary interaction with the participant but not to secondary research using the biospecimens.

Laboratory Developed tests - A laboratory developed test (LDT) is a type of in vitro diagnostic test that is designed, manufactured and used within a single laboratory. Laboratory-Developed tests (LDTs) do not currently require FDA oversight. (Source: FDA, 2018)

Laboratory Assays - An assay is an investigative (analytic) procedure in laboratory medicine, mining, pharmacology, environmental biology and molecular biology for qualitatively assessing or quantitatively measuring the presence, amount, or functional activity of a target entity.

- **Genotyping** –Genotyping is a technology that interrogates the presence of absence of a specific subset of genetic variants in a genomic DNA sample. It identifies primarily single nucleotide variations in genetic sequence in a DNA sample.
- **Sequencing** – Sequencing is a technology that determines the order of nucleotides in DNA or RNA. Sequencing includes single-gene assays, gene panel tests, exome sequencing, and genome sequencing.

    - **Exome sequencing** – sequencing of protein-coding regions (exons) of the nuclear genomic DNA, representing about 1% of the complete DNA sequence. Exome sequencing assays can include both nuclear and mitochondrial DNA. Mutations in regulatory regions that are noncoding are typically not detected by exome sequencing.
    - **Genome sequencing** – sequencing of nuclear or mitochondrial genomic DNA, most often by "Next-generation sequencing" or NGS. Genome sequencing is fundamentally similar to exome sequencing, or sequencing of any other subset of the genome by targeted capture techniques.
    - **Transcriptome sequencing** – sequencing of mRNA by NGS techniques.
    - **Targeted next generation sequencing** - focuses on specific regions of interest in the genome.
- **Methylation Analysis** – Methylation assays assess the status of specified methylation sites, most commonly in nuclear genomic DNA through methylation chip assay technology.

Variants – variant is the currently accepted term to describe the state of a nucleotide in a DNA or RNA macromolecule that differs from the reference sequence. This term is commonly modified with terms such as "rare" or "common", and/or "pathogenic" or "benign". For example, if the reference sequence harbors the C (cytosine) nucleotide at a specific base position in the genome, but a tested sample harbors an A (adenosine) at that position, the A is considered a variant.

- **SNPs** (often pronounced "snips") - are common single base-pair changes in DNA that occur at specific places in the genome. This term is falling out of favor, being supplanted by "common variant" as it has a number of associated connotations that are not always valid.
- **Mutation –** this is the former term for a rare variant, sometimes with a connotation that it is disease-associated. This term is being supplanted by "rare variant" or "pathogenic variant" or sometimes both. This term is the currently correct descriptor for the *process* of a nucleotide being changed from one base to another – a C to A mutational event.

Annotation – annotation of a genomic DNA variant comprises a variety of analyses and predictions regarding the molecular biologic consequences of the variant.

Classification – assessment of the probability of the validity of a variant-disease association for a specific genomic variant. (e.g., using ACMG/AMP Richards et al. 2015 recommendations to generate ClinVar entries.)

CLIA - Clinical Laboratory Improvement Amendments of 1988 (CLIA) regulations include federal standards applicable to all U.S. facilities or sites, that test human specimens for health assessment or to diagnose, prevent, or treat disease. The CLIA regulations specify processes for establishing performance characteristics of laboratory test, primarily analytic validity.

Laboratory-developed test - defined by the Food and Drug Administration as an *in vitro* diagnostic test that is developed and used within a testing laboratory. LDTs are considered devices and are subject to regulatory oversight by FDA; however, FDA has generally exercised enforcement discretion meaning that LDTs generally have not undergone FDA premarket review of analytic and clinical validity.

Primary finding – a finding in a clinical assay or test that is related to the indication for the assay or test and was purposefully sought by the analyst of the data.

Incidental finding – a finding in a clinical assay or test that is not related to the indication for the test and was not a finding that was purposefully sought by an analyst of the data.

Secondary finding – a finding in a clinical assay or test that is not related to the indication for the test but was purposefully sought in a systematic, directed analysis of the data.

Actionable finding – a finding in a clinical assay or test that has a reasonable potential to lead to a health care intervention that can reduce the morbidity or mortality of a disease.

Confirmatory testing – CLIA-compliant testing to confirm a screening test result or research finding.