2023 ASHG presidential address—Reflecting on our 75 years: Acknowledging our past, embracing our present, and dreaming about our future

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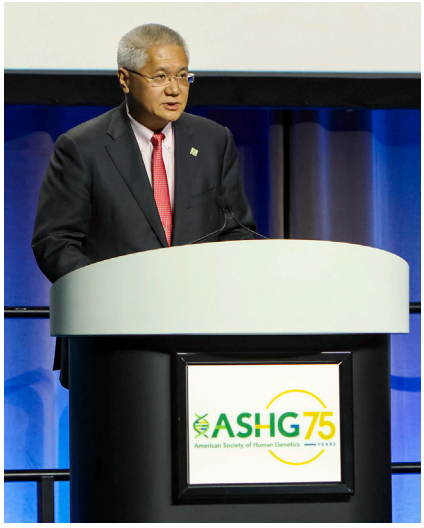
This article is based on the address given by the author at the 2023 meeting of The American Society of Human Genetics (ASHG). A video of the original address can be found at the ASHG website.



I am honored to have the privilege to serve as your president of the American Society of Human Genetics (ASHG) during this remarkable 75th anniversary year. I want to take the next 20 minutes or so to share my reflections on our past, our present, and our future. As you know the theme of this year's meeting is "one humanity, many genomes." I was delighted to hear when this was chosen. It made me think about its many layers of meaning. I'm sure it has done the same to you. On a literal genomic level—we of course share much more than what differentiates us—over 99.9% of our genomes are identical! However, as a medical geneticist, the small portion that distinguishes us can have real impact. For example, a single nucleotide change can cause a severe human genetic disease or confer disease susceptibility. As a scientific community, our goal is to understand these differences, target its biological impact, and fix the medical consequences or, at the very least, be informed by these differences for personal decisions. So, then how do we achieve one humanity? I would posit that the path is one informed by our shared journeys: by recognizing and learning from our history, by embracing our common present, and by dreaming together about our future. This shared journey is no different than the significant sharing of genomic ancestry. I would challenge all of us to carry this theme throughout the meeting and beyond in our everyday lives.

What a year it has been for ASHG! I started this 75th anniversary year much like all of you coming off the uncertainties of the first post-COVID year. For ASHG, this included regrouping from our first in-person post-COVID 2022 meeting in Los Angeles. I am delighted to report that the Society is healthy, has bounced back, and is in great shape. This is best exemplified by *your* outstanding participation here for the 2023 meeting! However, there continues to be challenges to our Society and our mission. The changing landscape in the scientific and funding arenas prompted us to revisit our strategic plan, primarily to update what was already an excellent pre-COVID strategic plan. The intent was to prioritize the existing goals for post-COVID realities. I am pleased to report that the work is largely complete, and the Board will soon release this refreshed plan (https://www.ashg.org/about/mission-strategic-plan/). It will be an important template to guide the work of the Society on your behalf.

We started the year unveiling what I view as one of the most important projects of the Society. Thanks to the leadership of multiple boards and an outstanding committee that led the work, the ASHG released the report of a multi-year effort: "Facing Our History—Building an Equitable Future."[1] In 2018, the ASHG Board established diversity as a top strategic priority and, following the height of racial and social unrest in 2020, it charged the Society to conduct a review of its own history. The report and its findings were *painful*.[2] It documents a history that must be told and taught so we can prevent its recurrence. By acknowledging our history and apologizing for wrongs, the Society seeks to form a stronger foundation for trust and inclusion in looking to the future. The Board in its immediate and future actions strives to ensure diversity and inclusion in all of our activities and commit to speaking out when harms are done due to the misuse of human genetics. I think the strength of the diversity

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https://doi.org/10.1016/j.ajhg.2023.12.020.

of ASHG is exemplified at many levels and in this meeting—by the diversity of participants, by the diversity of science presented, by the diversity of technologies exhibited, and by the diversity of topics discussed. It exemplifies our strength together.

In thinking about the shared journey of our Society members, I thought of my own personal and professional journey in the field of genetics and genomics. As a child immigrant, the product of chain immigration to the US, neither of my parents were college educated. I arrived in Houston 30 years ago this year for my pediatrics and genetics training and experienced firsthand how sequent epochs of technology innovation have driven discovery that have been presented every year since in this meeting. This is of course best exemplified in the transformation of sequencing technologies. As a graduate student, I cut my teeth on Sanger sequencing pieces of DNA cloned out of cosmid libraries and the PCR fragments to identify strong effect mutations in Mendelian phenotypes.[3,4] As arrays were developed, whole genome approaches for genome-wide association studies were possible to study common variants in common phenotypes, and now, whole-exome and genome sequencing for identifying strong effect alleles in common phenotypes and in phenotypic expansions in rare disease. This, of course, has had a parallel impact on the implementation of genomic medicine in the area of diagnostics, from sanger sequencing of single-gene disorders to chromosomal microarrays identifying copy number variations, to next-generation sequencing panels, whole-exome sequencing, and now whole-genome sequencing for diagnosing a wide range of pathogenic human variations. In the decade since, therapy for genetic disease in the form of viral and nucleic-acid-based gene therapy has become a clinical reality with now over 30 FDA approved *in vivo* gene and *ex vivo* gene-modified cell therapies primarily for genetic diseases and cancer (https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products).

Not surprisingly, ASHG's top milestones in human genetics and genomics (https://www.ashg.org/discover-genetics/timeline/) parallel this personal journey. The pillar is of course understanding and manipulating the structure of DNA and the human genome—from elucidating the double helix structure of DNA, to recombinant DNA approaches, to Sanger sequencing, to identifying markers of DNA, to the Human Genome Sequencing Project, to development of next generation sequencing, to gene editing, and to completion of high-quality genome references. Of course, applying this technology to understanding human variation was next: elucidating the number of single-nucleotide variations in the genome, discovering haplotypes of genetic variants that could be inherited, completing the 1000 Genomes Project, and developing reference population databases. The next two areas of course reflect the application of the first two by elucidating the genetic basis of disease and by using this information in health care. They very much reflect my personal scientific journey as this was and is the space I have had the good fortune of working. Most recent is then the appreciation of what is beyond DNA with application of technology to understand epigenetics, to cataloging all DNA elements that control gene expression and tissue-specific gene expression.

These epochs of technology innovation and milestones in human genetics have led us to this exciting meeting and our embrace and celebration of the present. Humans *are* the best model for discovery as human variation directly informs unique structure-function correlations in proteins and pathways.[5] It informs basic science, study of disease mechanisms, and drug development. An excellent example of this is the collaborative and multidisciplinary work of the NIH Undiagnosed Diseases Network.[6]

The application of transformative technology to diagnostics has and continues to be the best example of the benefits of our shared journey. This ranges from the use of WGS for diagnosing rare disease, to cell-free DNA testing in cancer and reproductive health, to the development of polygenic risk scores in common disease, to implementation of RNA sequencing and metabolomics in diagnostic algorithms.[7,8]

The understanding of the genetic basis of human disease and the underlying pathogenetic mechanisms and diagnosis of these disorders have empowered the application of gene therapy. It is not surprising that the American Society for Gene Therapy was in part founded by ASHG members who focused on therapeutic development over 25 years ago (https://asgct.org/about/timeline-history). Moreover, it is in genetic disease that we have had the many successful developments of gene therapy medicines from viral gene therapy for RPE65 retinitis pigmentosa and now spinal muscular atrophy, to cell-based gene therapy for beta thalassemia, to ASO therapy for Duchenne muscular dystrophy and hereditary amyloidosis, and soon-to-be-approved gene editing cell therapies for sickle cell anemia. This amazing "present," of course, is tinged by our challenges as a community in overcoming lack of diversity in research. This includes lack of diversity of patients in the form of health access disparity, diversity of participants for example in our genomic databases, and of course diversity of our workforce, as shown so clearly by the ASHG workforce survey. However, we are making progress, and this is well represented by the most diverse population cohort assembled to date in the All of Us research program,[9] as well as by initiatives such as H3 Africa (https://h3africa.org/) for building capacity for genomics and genetics in diverse communities and geographies. Our shared journey also includes facing emerging threats. No greater is the growing chorus of "anti-science" where increasingly vocal communities, including in policymakers, who reject science and the scientific method as an objective method that can generate universal knowledge for the good of humanity.[10] We must engage on this issue as citizen scientist, both as a society and in our everyday interactions with our fellow citizens.

What makes me most excited is the future of human genetics and genomics. There is no scientific field that moves as quickly and can change practice as quickly as human genetics and genomics! Our shared journey of the future must build on our history and the present to deliver the benefits of genetics and genomics to everyone everywhere (https://www.ashg.org/discover-genetics/forward-looking-advances-for-human-genetics-and-genomics/). It is to have equitable expansion of precision medicine. This means diagnosing every genetic disease and applying targeted treatments for all—all disease and all people. This also means integrating genomic information for health care and prevention for all. It is to increase diversity of genomics research. This means to have world-wide, equitable, and respectful representation in genomics. This also means to have world-wide participation in longitudinal biobanks in genomics. It is to develop new avenues for research and clinical impact. This means new approaches to treat and to test efficacy of treatments. It is to increase awareness of genetics. This means increasing education and awareness of public, health professionals, and policy makers to enable informed discussions and decision making about all aspects of society that are impacted by human genetics and genomics.

So how do we get there? Of course, adding to many genomes, we will need transcriptomes, epigenomes, metabolomes, proteomes, metagenomes, exposomes, secretomes, enviromes, microbiomes, phenomes, kinomes, and many more, to realize the promise of one humanity.

I want to end with some personal thank yous from my own personal journey that led me to the honor of presiding over this momentous ASHG year. I want to thank Baylor College of Medicine and the Department of Molecular and Human Genetics where I have spent my whole professional career. It is because of the faculty, staff, and trainees who are my colleagues, friends, and mentors that have anchored so many of us to this great environment of human genetics. I want to especially call out the late Ralph Feigin and Tom Caskey who convinced a New Yorker to call Texas home. I want to thank Art Beaudet my scientific mentor and chair at Baylor and who himself 25 years ago was ASHG President at the 50th anniversary. I want to acknowledge the late David Rimoin who was a professional mentor since I was a graduate student in NY. I want to thank my over 100 trainees and staff throughout my 25 years as an independent investigator—many of whom are here today. I want to thank my family who have allowed me the freedom to pursue the passion of genetics and genomics. And finally, I thank all of you, the human genetics and genomics community, who contributed to this shared journey!

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