ASHG Presidential Address: Who Is under the Umbrella—and Why Are We Here?

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Colleagues and friends—welcome to the 57th Annual Meeting of the American Society of Human Genetics. I thank you for the honor of serving as your president. We come together with good reason to celebrate: There has never been a better time for human genetics research. Genomic tools are providing us with new insights about genomic structure and gene function; the pace of gene discovery is faster than ever; and we now have a handful of innovative therapies based on genetic research, with prospects of more to come. This success derives in part from the wide range of research strategies that have been brought to bear on questions related to human genetics. It also reflects the dedication of our members. The success brings new—and welcome—challenges.

The fundamental goal of human genetics research is to develop new knowledge that will provide benefit to individuals, families, and society. In addition to excellence in research, our Society's vision statement calls for the translation of "new ideas into improved clinical practice."[1] An analysis by Gregory Treverton, from the field of strategic defense, provides a useful way of thinking about the challenges involved in this undertaking: Questions, he argues, should be characterized as either puzzles or mysteries.[2] The distinction offers an interesting perspective for human genetics.

A puzzle is a question that can be answered, given enough data. Where, for example, is Osama bin Laden? A puzzle has "already happened … the result has occurred, though it may not yet be known."[2] From this perspective, puzzles are the central concern of science. And scientists have had extraordinary success in developing knowledge about the structure of the environment, the physiology of living organisms, and the complex interaction between the two.

Over more than a century, researchers in human genetics have contributed importantly to this effort, taking on complex puzzles such as the laws of inheritance, the chemical composition of genes, and the biochemical basis of disease. One of the most recent and grandest successes, the Human Genome Project (HGP),[3] illustrates the iterative nature of scientific puzzle solving. The HGP could be envisioned only after the seminal discoveries of the mid-20th century: the DNA helix, the genetic code, recombinant DNA technology, and growing knowledge about the genomic structure of simple organisms.[4] Successful completion of the HGP required the solution of many smaller puzzles, including developments in technology that allowed for highly efficient sequencing.

A mystery, by contrast, is a question that cannot be answered with certainty.[2] Will North Korea keep its part of the nuclear bargain? Will democracy take hold in the former Soviet nations? Mysteries may reveal themselves over time and often have a preferred outcome. However, there is not, even in principle, a "right" answer because mysteries are based on complex situations for which the outcome is contingent, depending on the future interaction of many known and unknown factors.[2] The task in addressing mysteries is to identify and analyze the contributing factors, using expertise and judgment to identify actions that promote the best chances of a good outcome; in some cases, part of the mystery is to define what constitutes a good outcome.

The way forward in human genetics involves taking on a mixture of puzzles and mysteries. As we solve one set

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of scientific puzzles, we are able to tackle the next; at this meeting, for example, we see progress flowing from the use of genomic tools to identify genes, characterize their function, and lay the groundwork for a detailed molecular understanding of biological systems. However, providing benefit from this growing knowledge—and avoiding harm—takes us into the realm of mysteries.

For example, genome-wide association studies are achieving remarkable success in identifying gene variants associated with the common multifactorial diseases that account for the majority of the public health burden. These discoveries offer great promise through the identification of biological functions and pathways associated with disease, extending the benefit that genetic research is already providing for single-gene diseases.[5] Gene-disease associations can also be used to identify individuals at increased risk. Unlike the genotypes that account for classic genetic diseases, however, most gene variants associated with common multifactorial diseases have only a modest effect on phenotype. Their significance can readily be overestimated, particularly by media prone to exaggerating the causal role of genetics.[6]

Some of the complexities involved in determining the appropriate use of genetic susceptibility tests are illustrated by the genetics of age-related macular degeneration (AMD). As part of the recent wave of genome-wide association studies, several gene variants associated with either increased or decreased risk of AMD have been identified.[7,8] Although individual gene variants have limited ability to predict individual risk, combinations of variants can identify a small proportion of individuals with very high or very low risk.[8] Under what circumstances does a test of this kind provide clinical value? The answer to this question depends on many interacting factors, some of which are not yet defined, including the cost of testing, the safety, efficacy and cost of therapeutic options available to reduce risk or treat early disease, and the potential for discrimination, stigma, or exposure to unnecessary healthcare based on knowledge of genetic risk.

AMD is an early example of the opportunities and questions arising with growing knowledge of human genetics. Answers to the question of clinical utility will vary with differences in the predictive value of the test, disease severity, treatment options, and healthcare context. Uncertainties about risk and benefit are even greater for tests based on genetic associations with behavioral traits. These new testing opportunities will undoubtedly provide important healthcare benefits in some clinical settings; they are also likely to provide limited benefit or the potential for net harm in others.[9] The challenge is to define and consider the parameters that contribute to risk and benefit and to develop deliberative procedures to chart a responsible course forward. The questions involved are inherently transdisciplinary, requiring the sharing of expertise from fields as diverse as economics, law, ethics, psychology, education, medical anthropology, and sociology.[10] As with other mysteries, addressing these testing opportunities will require both data and judgment; policy analysis, ethical guidance and educational initiatives are all needed, informed by robust data on clinical, social, and economic outcomes.

This expanding research agenda comes at a time when review of genetic research is increasingly challenging for Institutional Review Boards (IRBs). The combination of genomic technologies, the creation of large biobanks, and plans for rapid data sharing pose new questions for IRBs. Experts are debating the preferred approaches to privacy protection, family-based recruitment, data sharing, return of results, and avoidance of group harm,[11–15] at a time when there is already evidence of considerable variation among IRBs in the interpretation of risks and benefits related to genetic research.[16] Two examples serve to illustrate the difficulty of the problems to be solved.

Exploratory research in human genetics is typically done with the understanding that individual research results will not be returned to participants. This approach is ethically sound when the data produced by the study are preliminary or not yet validated. But when data generated have clear clinical significance—as, for example, when a genomic study reveals a mutation associated with Lynch syndrome, thus identifying the participant as someone who would benefit from early and frequent colon cancer screening—researchers arguably have a moral obligation to disclose results.[13] When genomic research is based on shared data from large repositories, fulfilling such obligations is logistically difficult and may be possible only with planning and dedicated resources. For reasons of participant protection as well as research efficiency, careful thought needs to be given to the data characteristics that might mandate the return of results. This question parallels the clinical utility issues raised by genetic susceptibility testing: What genetic-risk information matters? And should the threshold be higher for research disclosure than for clinical use? A broad consensus is needed, taking into account both the well-being of research participants and the requirements and beneficial potential of good science.

The issue of group harm is another area requiring deliberation. Recent events—such as the use of data collected from members of the Havasupai tribe for purposes not authorized by the tribe,[17] and the claim (now refuted) that a gene variant putatively associated with brain development was selected for in European and Asian but not in African populations[18]—generate legitimate concerns about how genetic research will be conducted and interpreted. Our Society's mission includes promoting "responsible social and scientific policies"[1], and our code of ethics calls for a commitment to building public trust through accountability.[19] We have an obligation to ensure that all groups in our society benefit from human genetics research. As a corollary, we need to help craft research strategies that provide appropriate protection to groups as well as individuals,[14] guard against discriminatory and defamatory uses of genetic data, and speak out when science is misinterpreted or misused.[20]

Our Society can take a leadership role in resolving new and challenging questions related to responsible human genetics research and practice, along with partners in our sister genetics societies. An important component of this effort is to overcome communication barriers, ensuring effective dialogue among basic and clinical researchers, clinicians, community partners, and the host of disciplines involved in addressing social and policy issues. Our success in attracting an expanding number of disciplines under the Society's umbrella is a promising sign. About 7% of our members list ethics, social, legal, and policy issues as their primary interest area, 4% list public health genetics, and 2% list DNA forensics. These statistics point to the growing societal importance of human genetics. Another indicator is our Society's support of policy initiatives, including policy statements on topics such as direct-to-consumer testing,[21] support of legislation such as laws banning genetic discrimination, and joint efforts with the National Human Genome Research Institute and the Centers for Disease Control and Prevention to create policy-oriented fellowships.

Moving forward, we need to forge collaborative partnerships to promote the wise use of genetic knowledge. As part of this effort, we need to be sure our umbrella is big enough to make room for everyone who shares our vision. For the past two years, our Society has extended a special welcome to advocates for families living with genetic disease. Our educational programs have sought to reach out to students from diverse backgrounds and to provide assistance to teachers working in poorly resourced classrooms. Are we doing enough? Science will always be at the core of our mission, but ensuring the benefits of science requires that we acknowledge the mysteries arising from our work and the many partnerships that will allow us to address them. We need to create a common language that enables us to share expertise across a broad range of experiences and perspectives, promote science education, work in partnership with advocates and research participants, and expand the scope of our research to ensure meaningful assessment of societal benefit. These challenges represent a new wave of opportunity for our Society.

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