2016 Presidential Address: Let's Make Human Genetics Great (Again): The Importance of Beauty in Science[1]

Harry C. Dietz[2,3,*]

Good afternoon. As president of the American Society of Human Genetics (ASHG), it is my pleasure and privilege to welcome you to the 66th annual meeting of our society. It is a particular joy to join you in this beautiful venue in the spectacular city of Vancouver. This eighth visit of ASHG to the great country of Canada marks a particularly important time to acknowledge and applaud the essential contributions of our international colleagues to the vibrancy and relevance of our society. In broader terms, the ability of human genetics as a discipline to deliver on the promise of improving health and wellbeing worldwide in an equitable, just, and sustainable manner will require an unwavering commitment to collaboration, respect, and cultural sensitivity within our community. In this spirit of tearing down all walls, it is a distinct pleasure to welcome scientific and medical colleagues and trainees from over 66 countries to this meeting. I strongly encourage everyone from everywhere, but particularly the young people, to gather often in large and unruly groups to celebrate diversity and conspire to do great things together.

In keeping with this eye to the future, the themes of collaboration and mentorship will be emphasized throughout this meeting. Elaine Zackai will be the recipient of the inaugural ASHG Mentorship Award. I could not imagine a more worthy choice than a consummate clinician educator who integrates the basic and clinical sciences to serve and inspire her patients and trainees alike. In the Presidential Symposium, titled "Mentoring in a Challenging Environment," Huda Zoghbi, Lon Cardon, and Kym Boycott will share their perspectives regarding what it will take to prepare the next generation of human geneticists tasked with realization of the full potential of precision medicine.

In partnership with the European Society of Human Genetics, a joint Building Bridges session will address navigation of career paths in human genetics. Under the expert guidance of Chair Tony Antonellis, this year's ASHG Program Committee has fashioned an agenda that is both innovative and responsive, including implementation of specific recommendations of a task force requested by ASHG membership, convened by the ASHG Board, and led by Dian Donnai to enhance the integration and presentation of clinical content at our annual meeting.

As you will hear about in greater detail at the business meeting on Friday, our society remains financially sound, strategically engaged, and broadly relevant. In recognition of the leadership position of our society worldwide and the increased complexity of policy issues related to the development and application of genetic technologies, the sharing of genetic information, and the protection of genetic privacy and against genetic discrimination, the ASHG Board established the position of Director of Science Policy and recruited Derek Scholes, a graduate of our joint policy fellowship with the National Human Genome Research Institute, to help shape the policy platform and craft the public voice of ASHG. Over the past year, the opinions of our membership have been heard on many

[1]This article is based on the address given by the author at the meeting of the American Society of Human Genetics (ASHG) on October 18, 2016, in Vancouver, Canada. The audio of the original address can be found at the ASHG website.

[2]Howard Hughes Medical Institute; [3]Institute of Genetic Medicine, Departments of Pediatrics and Medicine, Johns Hopkins University School of Medicine, Miller Research Building, Room 539, 733 North Broadway, Baltimore, MD 21205, USA
*Correspondence: hdietz@jhmi.edu

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issues, including germline gene editing, the Genetic Research Privacy Protection Act, the Canadian Genetic Non-Discrimination Act, FDA oversight of next-generation-sequencing-based diagnostic testing, and expansion of NIH funding, to name a few. ASHG has expanded its reach with regard to the education of non-genetic healthcare professionals, including the development of teaching programs and tools, the formation of strategic relationships with academic, industrial, and institutional partners, and the launch of the Genomic Medicine Education Consortium to fund educational initiatives and ensure the vitality of the ASHG mission over the long term. ASHG leadership continues to explore mechanisms to enhance the diversity of and better serve our membership. A recent example is the expanded role of trainees in the business of our society, including full voting representation on the board and inclusion on virtually every ASHG committee. Our communications office seeks to reach out to members in new and creative ways that maximize engagement, informational content, and discourse. As always, we welcome your input and ideas both at the business meeting and at ASHG NEXT, a strategic planning session where members and society leadership will review progress on the 2013 strategic plan and consider new priorities and initiatives.

All right, with that out of the way, let's address the 900 lb gorilla in the room—that unfortunate title, "Let's Make Human Genetics Great (Again): The Importance of Beauty in Science." First lesson for future ASHG presidents: keep your wits about you when you get the email from ASHG staff stating that the program goes to press in 10 min and that they really need the title now. Second lesson: humor in desperation rarely works. In all fairness, there is an embedded message that I feel strongly about. Human genetics has consistently remained a great, highly innovative and broadly impactful discipline since its inception, variably placed at somewhere between the last 60 and 150 years, depending on your perspective. This has been accomplished by consistently rising to the occasion—by pulling the proverbial theoretical or technological rabbit trick when the field was stalled or the way forward was less clear. I would argue that human genetics remains great today by virtue of our communal ingenuity, productivity, and resolve.

I might also argue that there is a little more introspection and a little less swagger in our field at the moment as a result of both external criticism and internal ambiguity; in essence, it's again time to work our magic.

I can vividly remember the first ASHG meeting that I attended. It took place in my home city of Baltimore in 1989. The air was thick with excitement sparked by the recent success of positional cloning in humans, exemplified by the identification of the cystic fibrosis gene.[1] To a pediatric cardiologist in training with a recent commitment to better understanding and serving people with Marfan syndrome, the allure was undeniable. Amazingly, these scientists (read alchemists) could use tractable methods to achieve a definitive foothold in the pathogenic sequence for a previously mysterious disorder. Analogous to the development of the inexplicably powerful methods of quantum mechanics in the early 20th century, these theoretical and technical advances in genetics set the stage for even novices in the field to make meaningful contributions—my kind of place, I reasoned.

An immersion in the history of genetics revealed to the impressionable me, and to the jaded me even now, a sense of beauty in science that I had not experienced since junior high physics. The simplicity of Newton's laws, Mendeleev's organization of the periodic table of elements, or Bohr's model of the hydrogen atom made their ability to reconcile or even predict experimental observations, such as the motions of the planets or chemical properties of imaginary substances yet to be observed, all the more astounding. To fully appreciate that, when combined, the audacious deductions of Darwin and the rigor of Mendel established the foundation for full conceptualization of modern biologic reasoning was equally inspiring.

To learn that both weathered criticism in their time—Mendel by the suggestion that he additionally study hawkweed before making too much of a fuss out of his pea experiments and Darwin by the likes of Lord Kelvin, the greatest natural philosopher of his age, who was equally great at underestimating the age of the earth and hence the plausibility of natural selection—made me cheer.[2] The prescient sentence in Watson and Crick's one-page paper describing the structure of DNA, "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material," made me laugh out loud.[3] Together, this sentence and the opening comments essentially dismissing structures proposed by Pauling or Fraser created a sense of something uniquely beautiful, a sense of triumph complete. Considered in the context of Rosalind Franklin's critical contributions, this makes my 20th century scientific all-star list, which also includes Einstein's general relativity, Dirac's electron equation, Brenner and Crick's frameshift experiments defining the triplet nature of the genetic code, and their independent intuition regarding the essential existence of messenger and transfer RNA. Honestly, if I were fully aware at the age of 13, my bedroom wall would have included posters of Mickey Mantle, Angie Dickinson (as a policewoman), *and* Sydney Brenner. Strange, but true.

Looking back, I am awed by the advances made in our field over the past 25 years, their impact on biology and medicine, and the general character of their practitioners. I am immensely grateful for the welcome that I received by colleagues at Hopkins, including Victor McKusick, Haig Kazazian, David Valle, Clair Francomano, and Reed Pyeritz, and for the sustained mentorship and friendship afforded by others, notably Barbara Migeon, Aravinda Chakravarti, Gary Cutting, Peter Byers, and Francesco Ramirez. From my first ASHG meeting or Annual Short

Course on Medical and Experimental Mammalian Genetics, the immediate sense, the prevailing sense in our field, was one of both unprecedented opportunity and unavoidable obligation. We can and will revolutionize biology and medicine. There is work to do. Let's do it together. Get to work.

Great work was done, and beauty was apparent. Mysteries of inheritance were decorated with names and mechanisms such as mosaicism, imprinting, anticipation, or copy-number variation. Mendelian disease genes came in a trickle—and then a torrent—often informing the diagnosis and occasionally the management of rare conditions or even more common but complex presentations of component phenotypes such as atherosclerosis, arrhythmia, or seizures. We learned to expect the unexpected, including the realization that our gut flora deserves an opinion, that there is such a thing as too clean, and developmental disability can be reversible. Reproductive options were greatly expanded, and reproductive outcomes improved. We learned about who we are and how we got here, both figuratively and literally.

Perhaps our accomplishments over the last few decades will be best remembered, and most favorably judged, by the remarkable ability of our technological advances to meet and exceed our insatiable cry for more—more polymorphic markers with more inherent informativeness; markers with less informativeness but many more of them; more sequence; more sequence for more species; more sequencing capacity; more coverage of the exome; more than the exome; more sample size; more cohorts; more powerful analytical methods; more reference databases.

On this 18th day of October, 2016, I am pleased to announce that we have more—and it is good. But there is more work to do. Let's do it together.

In assessing our progress and prospects, I found it quite revealing to review the presidential addresses of three pioneers in our field—three early thought leaders and three of my heroes: Victor McKusick, Barton Childs, and Arno Motulsky.[4–6] All three predicted the so-called "medicalization" of human genetics as both inevitable and a virtue. In 1974, Victor noted that "medicine has given focus, direction, and purpose to human genetics" and that "this synchronization has occurred … without any weakening, indeed with strengthening, of the basic science foundations of the field." To the list of fundamental questions upon which the practice of medicine is based—what is wrong (diagnosis), what is going to happen (prognosis), and what can be done about it (treatment)?—he added, why did it happen? The answer to this paramount question in our field is the basis of "both prevention and scientific progress." He stated that "if expression of a mutant gene were quantitatively and qualitatively identical in all cases, medical genetics would, relatively speaking, be child's play. Learning medicine … is largely a matter of learning how to cope with the variability in the clinical effects of given etiologic agents."[4]

In 1976, Barton defined disease as "a state of individual homeostatic abnormality." He argued that "such a definition places disease squarely where it should be—in an evolutionary and social context." This "view of disease as an aberration of adaptation in the face of conditions which are suboptimal, not necessarily for all, but for [at least] one genetically and socially distinct individual" highlights the shortcomings of a purely statistical standpoint and offers the potential to "transcend the conventional restrictive concept of etiology."[5] Barton's address was a tough but highly memorable read with a density of ideas that was admirably matched by clarity of thought. It was with both joy and remorse that I remembered him at every morning report and case conference during my pediatric residency asking, "Why is this patient with this disease presenting with this problem at this time?" The joy relates to my current admiration for his insight and persistence; the regret—to the shrugs and (un)knowing glances shared by me and my fellow trainees in the face of sleep deprivation and the pressing need to catalog lab results and write discharge summaries.

In 1977, Arno contended that "in view of the complexity of genetic and environmental factors involved, a Mendelian approach which attempts to isolate individual gene action in the multifactorial common diseases and normal behavioral traits is simplistic." To an extent, he argues, prevailing practices were related to the pragmatic choice of scientists to address "nontrivial problems [that could] be solved by existing concepts and methods." In essence, if biochemistry is the "art of the soluble," then human genetics is the art of the statistically tractable. Despite such limitations, Arno counseled that "spectacular" results in etiologic understanding could be achieved when human genetic observations were combined with those of other fundamental basic sciences, for which he cited the synergistic contributions of McKusick and Neufeld in unraveling the mucopolysaccharidoses as an example.[6] What Victor and Barton and Arno were telling us, and what others since have echoed, is that it is really complicated, that the devil is in the details, and that our field avoids the tenet that biochemistry or biology (of the cell or developmental types) should be on at least equal footing with Bonferroni at its peril.

I have also given extensive consideration to the needs and wisdom of my patients with a genetic predisposition for disease. When we first identified that mutations in the gene encoding fibrillin-1 cause Marfan syndrome, a multisystem connective tissue disorder associated with skeletal deformity, ocular disease, and a severe risk of early death due to aortic root enlargement and rupture, we anticipated that the uptake for prenatal or preimplantation genetic diagnosis would be high. As it turned out, however, many patients were ambivalent or even strongly disinterested. To an extent, this was most likely related to improved medical and surgical management of the cardiovascular manifestations of this condition. Tellingly, the greatest enthusiasm for assisted reproduction to avoid

Marfan syndrome in future generations came from individuals with the most severe features that had the greatest potential to negatively influence their quality of life, such as those in the skeletal and ocular systems, but not necessarily longevity, such as those in the cardiovascular system.

Early in my career, I can remember meeting with the parents of a newborn son named Monty, who was diagnosed with the most severe and rapidly progressive form of Marfan syndrome, typically associated with death due to congestive heart failure within the first year of life. In contrast to my expectation, the conversation focused on the prospect of relatively small but cumulatively important triumphs: might he live long enough to know his sisters, graduate kindergarten, kick a soccer ball? Although this could have been attributed to being overwhelmed or naive, this tone, this sense of pragmatic compromise, this satisfaction with minor miracles was maintained throughout Monty's overtly challenged yet unexpectedly long and wholly wonderful childhood.

As a member of the Professional Advisory Board of the Marfan Foundation for the past 25 years, I was initially perplexed but am now inspired by the call of our constituency to give higher funding priority to research focused on mitigating foot pain or headache frequency or fatigue or social stigmatization. In essence, they asked, can you help us live better with our condition—to more robustly align our predetermined genetic allotment with the conditions with which we live? To a meaningful extent, such issues have remained in the exclusive purview of our medical subspecialty colleagues. Can and should human genetics have more to say on this matter? Extending beyond diagnosis, prognosis, or prevention gets us back to McKusick's fourth question (why did this happen?), to Child's query (why to this [but not that] person, and why now?), and to Arno's counsel (understand "the fundamental science base of these conditions"[6]). Beyond variants that are benign or pathogenic, they would argue that we need to acknowledge and master "variants of variable significance," because therein lies our leverage.

The two obvious factors to consider are environmental and genetic modification of phenotypic expression of a predisposing genotype. Although both are equally formidable issues to address, we have had much more success with the former than the latter. Examples include gene-environment interaction in obesity, susceptibility to infection, asthma, allergy, psychiatric disease, and cancer. Success in elucidating such interactions might be informed by consideration of disease in an evolutionary context. If we attempt to reconcile, in environmental terms, the signature for Darwinian selection of alleles with known biochemical or biologic but not phenotypic consequence, insights regarding disease mechanism and treatment in modern times might become apparent. The reverse of this strategy—explaining known disease allele frequencies by inferring interplay between gene function and historic conditions—has been commonly applied. Cystic fibrosis, diabetes, and sickle cell disease come to mind. The same cannot be said for a more nuanced forward approach. An illustrative, if not entirely chronologically accurate, example might be the following: (1) Tibetans have a remarkably high frequency of an allele encoding the p.Cys127Ser gain-of-function variant of PHD2. (2) PHD2 degrades HIF, a factor that normally augments erythropoiesis. (3) This allele in Tibetans protects from altitude-induced rise in hematocrit and fetal loss. (4) Therefore, involvement of the PHD2-HIF axis should be explored in various presentations of anemia or polycythemia, and its modulation holds promise in the treatment of a variety of diseases, including primary hematologic, thrombotic, and ischemic conditions (adapted from Lorenzo et al.[7]).

Another underemployed approach is to understand remarkable escape from disease despite overt environmental exposure. Instead of asking, for example, what alleles predispose to type II diabetes or smoking-induced lung cancer, the signals might be fewer but stronger, the requisite sample size lower, and the therapeutic relevance more direct if we look for variant enrichment among hearty obese or elderly 80-pack-year individuals.

Examples from our own work have highlighted the potential for serendipity or clinical observation to inform gene-environment interactions and therapeutic opportunities.[8] While studying the ability of various classes of antihypertensive agents to modify the aneurysm phenotype in mouse models of Marfan syndrome, we observed that calcium channel blockers unexpectedly led to hyperacute acceleration of aneurysm growth and tear, literally tripling aneurysm size within 5 weeks and causing death due to aortic rupture within 6 weeks of treatment initiation. Mechanistic characterization led to appreciation of a pathogenic role for the PLC-IP3-PKC axis and a protective role for the PKC inhibitor enzastaurin in Marfan mice that had—or had not—received calcium channel blockers. A subsequent retrospective analysis of Marfan-affected people who were taking calcium channel blockers at the time of enrollment in the GenTAC database revealed an odds ratio of aortic dissection or aortic surgery during the follow-up period of 12.5 or 5.5, respectively.

More recently, we focused on the high risk of aortic dissection in Marfan-affected women who choose to become pregnant. Although dissections have historically been attributed to increased hemodynamic stress, it seemed odd that the majority occur within the first few weeks after delivery. This led to the hypothesis that the hormone oxytocin, which peaks at the end of pregnancy and is maintained at high levels during breastfeeding, might be a contributing factor. Informatively, a Marfan syndrome mouse model that shows near-complete death due to aortic rupture in the early postpartum period is largely or completely rescued by avoidance of lactation or administration of an oxytocin receptor blocker,

respectively. The lesson, I think, is that clues and opportunities are all around us but that we need to engage the expertise and enact the inclination to recognize and exploit them.

The promise of elucidating gene-gene interactions in efforts to understand the inheritance, pathogenesis, and treatment of disease has been hotly debated. Although the additive effects of the individual influence of variants at two or more loci have been documented by both modifier and genome-wide association studies, the mere existence of non-additive synergistic effects—so-called "true" or "physiological" epistasis—in humans remains controversial. Weinreich defined epistasis as "our surprise at the phenotype when mutations are combined, given the constituent mutations' individual effects."[9] In view of how many surprises in human phenotypic expression remain unresolved, among which is "missing heritability," the prospect (perhaps inevitability) of human epistasis should not be dismissed.

Indeed, given the ubiquitous nature of epistasis in model organisms and the fundamental biological foundations for its existence, the absence of epistasis in humans seems illogical, or at the very least unfair. In the words of Einstein, "the Lord is subtle, but not malicious." I have to admit that in my frustrated attempt to understand the mathematical nuances brought to bear on this issue, I became obsessed and inordinately distracted with the task of finding an eminently accessible and unequivocal example in the context of human disease. I thank Andy McCallion for bringing the example of Rotor syndrome, a form of hyperbilirubinemia, to my attention. Rotor syndrome is a true digenic recessive trait, where biallelic loss-of-function mutations at independent loci are required for any evidence of biochemical or clinical expression.[10] This seemed like a major triumph at the time; perhaps more importantly, its recognition allowed me to resume work on this address.

Using particularly cogent reasoning and citing low and/or skewed allele frequencies, small effect sizes, linkage disequilibrium, noise, model complexity, and limiting sample size as potential confounding variables, Haley and Hartl argue that failure to detect a signature for so-called "statistical epistasis" at the population level does not infer the lack of influence of genotypic context on the individual (i.e., physiologic epistasis).[11,12] Haley suggests informed candidate-based studies as a path forward. From a patient-centric viewpoint, differentiation between additive and true epistatic interactions seems unnecessarily contrived. Their fundamental question is whether an actionable aspect of genetic context, given their primary predisposition, can prevent, delay, or in some way mitigate attainment of a functional threshold for phenotypic expression.

Two particularly beautiful recent examples of achievement in human genetics come to mind: those of PCSK9 and BCL11A. The PCSK9 story begins with the demonstration of recurrent mutations with the genetic and subsequent biochemical signature of gain of function in familial hypercholesterolemia. It was subsequently shown that common hypomorphic variants and rare or induced loss-of-function alleles in both humans and mice associate with low levels of low-density lipoprotein (LDL) cholesterol and protection from coronary artery disease in the face of overt environmental and/or genetic predisposition. The heartiness and fertility of an individual compound heterozygous for loss-of-function *PCSK9* alleles (with LDL cholesterol of 14 mg/dL) highlighted the safety of therapeutic strategies aimed at antagonizing PCSK9. Subsequent studies have suggested that, no matter what life throws at you (Big Macs, predisposing alleles, or both), PCSK9 antagonists hold promise to improve the length and quality of life through prevention (and perhaps even reversal) of atherosclerosis.[13]

The BCL11A story begins with a quantitative trait locus (QTL) association study to identify genetic determinants of postnatal production of fetal hemoglobin. Although expression of fetal hemoglobin is typically restricted to fetal life, decades of investigation had shown that it could modify the severity of various hemoglobinopathies, including thalassemias and sickle cell disease. Low expression or loss-of-function alleles of *BCL11A* associated with persistence of fetal hemoglobin, amelioration of beta-thalassemia, and productive modification of outcome parameters, including the frequency and severity of pain crisis in sickle cell disease, allowing conceptualization of a mature therapeutic strategy.[14]

The bottom line in both of these stories is that effects of variation at one locus were both predicted and observed to modify the clinical outcome of predisposing variation at another. By mimicking nature's success in the form of pharmacologic agents or perhaps genome editing, real progress will be made. Importantly, it took the likes of Hobbs and Orkin, among others, with diverse expertise and career-long investment in the problem, to fully prosecute early leads. Given favorable circumstances, it seems possible—even likely—that similar approaches might link QTLs for bone mineral density, oxygen diffusion capacity, or serum creatinine with revolutionary treatments for osteoporosis, emphysema, or skeletal myopathies, respectively, as just a few examples.

I began by dismissing the faulty proposition that we need to make human genetics great again. Rather, we as a society and we as a community are collectively blessed with a diversity of talents and the creativity and resolve to meet all formidable tasks ahead—to display our greatness *once again*. The call for "more" might need to be supplemented by a quest for better—better cohorts with better capture of granular phenotypic and environmental information that is better tailored to the specific question at hand, as well as better integration of the clinical and basic scientific acumen within our discipline and beyond. We also need to demand academic models that foster and reward cross-disciplinary collaborations and funding priorities that equally nurture big science and the next big thing that lingers in the

imagination of our extraordinary individual young investigators. I end firm in the conviction that *we are stronger together.*

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