2014 Presidential Address: The Time of Our Lives[1]

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Good afternoon, and welcome to San Diego and the 64th meeting of The American Society of Human Genetics (ASHG). It's my privilege to stand before you today as the president of this society—truly an honor and a dream—a dream that I hope some of you here in the audience might dare to dream, because it is truly a dream worth dreaming. Beginning with the first meeting I attended in 1979 in Minneapolis, being a member of this society has been one of the most treasured aspects of my career as a human geneticist. I am very grateful to Walter Nance, chair of the Department of Human Genetics at the Medical College of Virginia during my tenure there as a graduate student, for making this meeting an integral part of our graduate-student trainee development as human geneticists. With the exception of the international meeting held in Washington in 1991, during which time I was in labor and delivery at Brigham and Women's Hospital in Boston, it has been my special pleasure to be present at all of the meetings since 1979. I have countless wonderful memories of the meetings over those years—of the science and of the friendships—and I can assure you that this meeting will be no different, and I will speculate that it might even exceed your expectations! Many thanks go to all of those who have worked tirelessly to make this 64th annual meeting possible, especially to the ASHG staff and the members of the program committee.

I'd like to offer a special welcome to all trainee members who join us for this meeting; you are the future of this organization that we so cherish. Trainee badges have a special designation so that you will be able to find each other throughout the meeting. Thank you for being with us and for preparing for the roles you will have in this society. Be sure to join us at the business meeting, where you will hear reports of the society committees.

Next, I'd like to extend a warm welcome to all of our international attendees. Many of you have traveled great distances and processed considerable paperwork to be with us on these shores, and I thank you deeply for your efforts because we strive to be a society of human geneticists who appreciate the privileges and challenges of the work before all of us as a global community. Despite the daily sadness from the news of the many current struggles of humankind, in this hall we have the freedom to join together on common ground for a common glory—we share the language of science, we treasure the diversity of our cultures, and we have hope and responsibility for our discipline to bring improved health to future generations of the residents of planet Earth. As human geneticists, this is "the time of our lives," and the phrase, "To whom much has been given, much is expected," echoes through my thoughts in so many dimensions.

On a personal note, writing this presidential address has been a journey for me, and I imagine that sentiment is shared by many past presidents, who have frequently asked me when I have been in their presence, "How's the address coming"? I found myself replying to each of them, who happened to be men, that for me, it was not just about the address, but as a woman, it was also about the dress! As I labored over this task, I realized that the requirements for this address could include being entertaining, uplifting, visionary, and personal—that it is not only about "the time of our lives" but also

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about "the time of my life" as a human and medical geneticist.

Communication and Collaboration for a Common Glory

My remarks today will be centered in part around a theme of communication and collaboration…for a common glory. The phrase "common glory" is a special one to me as a graduate of the College of William and Mary in Virginia. On campus, an outdoor theater backing up on Lake Matoaka was the site for 30 years of a Paul Green symphonic drama entitled *The Common Glory*. Produced by the Jamestown Corporation, it tells the story of the American Revolution. As I think ahead for our discipline and our society, I have great excitement and hope for our common glory.

Opportunities of the Omics Era and Precision Medicine

There can be no doubt that we are living at an unprecedented time in the history of biology and medicine.[1] The exploding access to big biological data, and lots of it, from individuals with clinical phenotypes and to their disease (or health) outcomes will inform our knowledge. Insights into frightening infectious diseases, such as the current Ebola epidemic, are being made through genomic approaches that make it possible to assess how the virus is evolving to improve current diagnostic tests and to guide work on vaccines and treatments. Individualized therapies and new targets for drug development are opportunities to improve medical management. Ever enlarging data sets about our biology will be the drivers of the future of medicine.

Part 1: Mapping the Human Genome

I fondly recall presentations by Victor McKusick about our role as cartographers—our task was to construct the map of the human genome—and for decades he was certainly the master curator of that map. I owe a special thanks to Victor with regard to my personal involvement in gene mapping. It was during the 1981 Annual Short Course on Medical and Experimental Mammalian Genetics (by the way, this has been a destination stop for human geneticists for 55 years now) that I met a postdoc of Philip Leder's, Lanny Kirsch, while assisting in an afternoon session where karyotyping using photos, scissors, and tape was being held. That conversation led to my learning chromosomal in situ hybridization and the mapping within the next year of the immunoglobulin heavy chain locus to 14q32 and of *MYC* to 8q24—and it "did not escape our attention" that there was a relationship with the t(8;14) in Burkitt lymphoma.[2]

Many of you will remember the fun of the days of the mapping meetings—days when we placed genes one by one on chromosomes, when we estimated the human genome to be composed of 100,000 genes, and when computer security was so unsophisticated that the editors of one chromosome committee could engage in a bit of mischief overnight by moving a gene onto another chromosome to the great surprise the next day of the editors of that chromosome. In retrospect, positioning genes on chromosomes appears to be a rather simple endeavor, especially now in view of the task of defining all of the variation in that map. Although the mapping meetings as such came to a natural end and genome meetings took their place, the map is surely yet to be finished, and a lot of fun remains to be had. But, what was this all about? It was about the coming together of a community and about our communication and sharing of the science of our discipline, whether in the afternoon of a session in Bar Harbor on karyotyping or in chromosome committees of the mapping meetings held around the globe.

Part 2: Understanding the Variation

An undeniable challenge faces us now as we strive to analyze immense data sets, extract useful information, and annotate DNA variants. We often struggle to provide an interpretation and find ourselves building the plane as we are flying it. But, in truth, this is not a new road for us to travel. As a human cytogeneticist for the past three decades, I have been in the position of providing information of uncertain clinical significance and of an incidental nature to couples after prenatal analyses. One such counseling session remains etched in my memory. I met with a couple who had amniocentesis for advanced maternal age of a treasured IVF twin pregnancy. The twins were op-sexed, and the male co-twin harbored a supernumerary inverted duplicated 15. This was a well-recognized chromosome abnormality, but in those days before any molecular analysis of this chromosomal aberration for clinical interpretation was available, the phenotype ranged from normal to abnormal. I telephoned Tim Donlon, one of my cytogeneticist colleagues who had a research interest in this chromosomal aberration, so that I would be current on the latest information. We discussed the importance of providing a balanced presentation of the scientific information and of supporting the couple in whatever decision they would make. We also spoke about the importance of conveying the potential severity of the disorder so that the counseling session might not be revisited in the future with a perception that I had not portrayed "how unfortunate" the outcome might be. I struggled with this thought and then worried after the session whether I had been too negative about the outcome from a self-defensive position. Later, I received a thank-you note from the couple, who informed me that they had decided to put all of the genetic information aside and to enjoy the remainder of the pregnancy. As could be reasonably expected, the baby was well at delivery, and I sincerely hope that remained to be the course of development.

There are several lessons from this case. First, as those of us who have the privilege to serve the public know so well, our patients recurrently teach us many poignant lessons of life, and we cannot anticipate the view they

will have of the information we impart to them. Although we are conscious of the reality that we do not walk in their shoes, we are constantly reminded of that fact. Second, and with relevance to the situation we find ourselves in today in interpreting genetic variants and in dealing with incidental findings, we have had a long history of delivering information that is of uncertain clinical significance and that is of an incidental nature. I believe we are prepared well for our position in this diagnostic space, and we will continue compassionately to strive to provide state-of-the-art knowledge to those who seek our assistance. But, it is our responsibility to improve that knowledge at the greatest possible speed. This will be a legacy of our times. How will we go about this task?

Part 3: Treasuring Your Exceptions

Let's return to the work of mapping (and annotating) the human genome. We are still in that business, and there is ample discovery yet to be made. And, we are skilled artisans at that task and have tools that allow us to decipher the underlying genetic etiology of the individual undiagnosed patient. From my earliest days as a human genetics graduate student, I became familiar with the words of William Bateson from his lecture *The Method and Scope of Genetics*, delivered in 1908: "If I may throw out a word of counsel to beginners, it is: Treasure your exceptions!" Individuals with chromosomal rearrangements, representing possibly n-of-1 experiments, have tremendous potential to tell us about the workings of our genome, as do patients with undiagnosed diseases.

Over the past decade, my collaborators and I in the Developmental Genome Anatomy Project (DGAP) have exploited the biological resource of apparently balanced chromosomal rearrangements in individuals with clinical findings to discover genes involved in human development. The endeavor began with fluorescence in situ hybridization mapping of breakpoints, followed by Southern blotting, cloning of rearranged DNA restriction fragments, and Sanger sequencing. The development of next-generation sequencing changed all of that, as it has also done for discovery of Mendelian disease. Now we can rapidly identify genes disrupted or dysregulated at chromosomal breakpoints. From a decade now of work in this project, I can assure you that in this approach, most of "the keys" (the genes) are under the "the lamp post" (the chromosomal rearrangement). Each subject can illuminate a pathway yet to be associated with a constellation of abnormal findings.

Spectacular advances in sequencing technologies have made possible translation of nucleotide-level resolution of chromosomal breakpoints into prenatal diagnostics. In the last 2 years, we have provided informed genetic counseling in six high-risk prenatal cases with de novo apparently balanced rearrangements—consistent with their normal array comparative genomic hybridization (aCGH) findings—whereas two decades ago, Dorothy Warburton's cytogenetic studies of a series of newborns with such rearrangements led to estimates of risk of an untoward outcome of 6.1% for a translocation and 9.4% for an inversion.[3] Two additional cases are underway. The second case in our series was a 41-year-old female whose fetus, at a gestational age of 16 weeks, had normal first-trimester screening and a de novo paracentric inversion of chromosome 8. Sequencing analysis revealed disruption of *KHDRBS3*, encoding an RNA binding protein involved in the regulation of RNA splicing. It gives me great pleasure to report that this male child is now 23 months old, and all developmental milestones are within normal limits, largely as a result of the advancements in technologies we have available to us at this time in our lives. Eighteen months after delivery, the mom and her son, Julian, made a video for us, and the mom stated, "If we were not here, if we were in some other place, most likely Julian would not be born."

The days of turning away from investigating a single rearrangement in a leukemia and requiring it to be consistent in a series of patients before it would be worthy of investigation are historical. So, I say, especially to my cytogeneticist colleagues in the audience, let's capture all of these exceptions that we have among our patients and make this invaluable contribution to rapidly annotate the genome. At this time in our lives, this is our obligation to the next generations. Etched on the wall in my home institution—Brigham and Women's Hospital—above an exhibit that housed the Nobel Prize awarded to Joseph Murray for leading the team completing the first ever human organ transplant were his words: "Service to society is the rent we pay for living on this planet." My fellow geneticists, I think the time is now that our rent is due.

Part 4: Sharing Data

I'll share with you one current example from DGAP because it brings into focus the value and complexity of communicating research results to participants and gives us pause to think about how the growing number of research results from genomic studies can be delivered in a responsible, timely, and cost-efficient way. It is certainly timely to think about data sharing given that the NIH has recently issued the Genomic Data Sharing (GDS) Policy.[4] Sharing of large-scale human and non-human genomic research data facilitates translation of research findings into understanding that can lead to improvements in human health. As a member of the Federation of American Societies for Experimental Biology (FASEB), comprising 27 scientific societies, ASHG has an important role in shaping science policy. We are pleased to have had an opportunity to provide comments and participate as a signatory on a response to the draft GDS Policy. Although the FASEB response commended the NIH for their leadership, concerns were expressed about the increase in administrative burden for investigators and institutions (certainly a sign of our times) and a potential decrease in human subject participation in clinical genomics research. Within the next month, ASHG will participate in providing feedback to the recently issued FDA Guidance

and Oversight Framework for Laboratory Developed Tests,[5] which no doubt is of great interest to many members of our society. Other regulatory issues, including new individual data-access rights created by changes to federal privacy and laboratory regulations, raise troubling questions for genomic testing. Furthermore, the FDA has reached out within the past year to researchers to assess whether investigational-device exemptions are required on the basis of the level of risk to participants.

Recently, I provided the research results from our studies of a subject (known as DGAP179) to a clinical geneticist for her to explain to the mom. The mom had sent me an email in May of this year to ask whether there were any results available on her son, who she had enrolled in DGAP in 2003 when he was a toddler. In a subsequent email, she stated that when she had attempted simple online web searches, nothing popped up when she entered "chromosomal translocation 2 and 13" except for several hits referring to a cancer. She had found hits for a well-known consistent rearrangement in alveolar rhabdomyosarcoma. She commented that they putter along from day to day while enjoying her son's charm and good nature, but that this past year has been characterized by frequent illness, and that she was overcome by a sense of urgency to find any information that would be helpful to her and to provide details that might be helpful to other families. We replied to her that we were working on this case, that there would be results to report to her in the future, and that we would be happy to explain experiments that were underway. This mom is a special-education teacher, and her son had been in her classroom for all of his elementary school days. He would soon move on to middle school, and she was struggling with the thought of no longer spending her entire day with him. Her son is nonverbal and non-ambulatory but extremely social, and she stated, "Everyone who meets him loves him." Her emails were filled with a mother's love and pride. In July, she wrote back to report that she had become Facebook friends with a mom whose son has Pitt Hopkins syndrome and that that mom had asked her whether she'd ever heard of Mowat-Wilson Syndrome, which she had not. She looked it up and stated that it could have been written about her son! Also, the images looked like they could be pictures of her son's long, lost siblings—and some of them could have been of him! She stated, "I really think this is us! Sorry for all of the exclamation marks—it's kind of where I am right now ;-). I put in a call to the genetics clinic of our children's hospital today and will anxiously await a reply. Though I'm scared it might be months before they can see us."

As the DGAP research evolved over the first decade of this century, we began to screen each de novo rearrangement with aCGH to uncover potentially any other genomic aberration that might have a role in the subject's phenotype beyond the apparently balanced disruption or dysregulation of a gene at the breakpoints of the rearrangement. We began our studies of DGAP179 in 2008 and performed aCGH in our research laboratory, where we detected two deletions believed to be pathogenic. A 1.7-Mb deletion on the long arm of chromosome 2 included *ZEB2*, a gene reported to be mutated in Mowat-Wilson syndrome, consistent with various clinical findings at enrollment of DGAP179. In addition, some clinical findings were atypical but perhaps not inconsistent with Mowat-Wilson syndrome. However, a 900-kb deletion on chromosome 11 also disrupted *CNTN5*. Although we had made an interpretation of the phenotype to be consistent with the deletion of *ZEB2*, we believed we needed to complete the sequencing of the translocation distant from the deletion before the case could be reported, and that only happened this year. Interestingly, the translocation between chromosomes 2 and 13 interrupts a transcript of the large intergenic noncoding RNA *LINC00333* and a non-genic region on the short arm of chromosome 2. So, it's a complicated "n-of-1 story" with two megabase-sized deletions and a translocation that disrupts a non-coding RNA. Explaining all aspects of the subject's phenotype with the genomic findings is not easy—certainly not simple to pass by any journal editors. That's my "excuse" for not communicating the results in a more timely fashion, but in doing so, it has been at the cost of depriving a loving mom a diagnosis, even if it is in this case an incomplete explanation of the clinical findings. I recall often the words of Di Donnai, who spoke on a panel at an ASHG meeting a couple of years ago: "Never underestimate the therapeutic importance of a diagnosis, even when there is nothing that can be done." But something could have been done in this case—the mom could have received support from other families with children with Mowat-Wilson syndrome, and I am sure that she would have benefitted from such friendships. I think differently now about the value of research results for patients from this recent experience. In addition, although the mom discovered the diagnosis of Mowat-Wilson syndrome herself, and then her son was seen by a clinical geneticist who agreed with her diagnosis, reporting the research finding of a deletion of *ZEB2* redirected the confirmatory test by a CLIA-accredited laboratory to aCGH rather than sequence analysis of *ZEB2*—another valuable contribution from communicating the research result.

I imagine that many of you are familiar with the story of Matthew Might and Cristina Casanova. Titled "One of a Kind,"[6] it was written this past summer by Seth Mnookin in *The New Yorker* and concerns a newly diagnosed congenital disorder of deglycosylation involving N-glycanase 1. There are many lessons therein, including yet another success of exome sequencing, but this report also illuminates issues akin to those in the DGAP179 tale. On a positive shared note, it reports how the use of social media can help families affected by rare diseases find other families (such as Facebook friends in DGAP179). In this article, a mom who attended a Rare Disease Symposium meeting stated, "It feels like we've come home, but to a home we

didn't know we had." In another aspect, it brings up the issue of sharing data with subjects—and I quote, "As a matter of protocol, researchers typically avoid sharing test results with subjects until the research is published"—and sharing data with competitors out of concerns about publication. Both are data-sharing issues of disservice to those who need our assistance. Now, I'll make a note added in proof of this address from reading a Commentary[7] in the October 2014 issue of *Genetics in Medicine* while on my flight from Boston to San Diego on Thursday. It is co-authored by Matthew Might and Matt Wilsey, both fathers of children with this same deglycosylation disorder. In the last paragraph, these dads speak to us: "When you have a bad day in the clinic or the laboratory, please remember that there are patients and parents out there who you do not know and who are dreaming of finding you, supporting you, and counting on you." Matthew and Matt, thank you both so much for these uplifting words. I assure you that assembled in this hall is a community of individuals committed deeply and on a daily basis to the challenges your families' stories have defined so well. You can count on us.

We must share the information we learn. Various efforts are underway and are addressing this challenge. Earlier today, the Global Alliance for Genomics and Health held its second plenary meeting here in San Diego. The Global Alliance, founded just last year, is an international coalition working to enable the sharing of genomic and clinical data. Its over 220 partners are dedicated to improving human health by maximizing the potential of genomic medicine. ASHG is proud to be a founding partner of the Global Alliance, and many of our members are active participants in its working groups. We believe that this international partnership will be highly effective in unlocking potential advancements in human health, and we're excited to join with hundreds of diverse leaders in healthcare and biomedical research, patient and disease advocacy, and life science and information technology. By sharing data, we can all do our part to hasten knowledge growth and improve medical outcomes.

Part 5: Ending with a Surprise

I want to thank all of you, for as members of ASHG, you made it possible for me to carry two of the best business cards that I could ever have dreamed to have in my pocket—as your 2014 president and as the editor of *The American Journal of Human Genetics*. I also want to mention three wonderful mentors who were instrumental in the passages in my career from graduate school to postdoc to faculty. These three individuals are an all-star group, and I am ever grateful to the guidance of Walter Nance, Philip Leder, and Ramzi Cotran. Then there are those with whom I trained and those whom I trained; you all know who you are, and I hope you know how much I appreciate your friendship and support over these many years. I'd also like to mention Katy Phelan, who was my roommate in graduate school and who has roomed with me at countless ASHG meetings since the first meeting we attended in Minneapolis in 1979. Lastly, I want to thank my family: my husband, Bill, my son, Russell, and my daughter, Emily, shown here on a trip to the Galapagos Islands, where once more in life they were accommodating in some way their family geneticist—this time on a pilgrimage she had to make.

Now, it's really that time to wrap up one more presidential address. Let's think about the exciting meeting ahead of us this next week and the special colleagues with whom we will have "the time of our lives" and share a "common glory." My surprise ending is to close with a clip from *The Common Glory*. Let's communicate, collaborate, and share a common glory!

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