Predictive and Precision Medicine with Genomic Data

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Genome and exome analyses have become instrumental in establishing genetic diagnoses for critically ill newborns and in cases of previous diagnostic dilemmas. Genome and exome sequencing of presumably healthy individuals is now gaining traction. The roll-out of genomic medicine to the generally healthy population offers a new opportunity to provide insights into the current and future healthcare of individuals and their families. Indeed, numerous projects such as Geisinger’s MyCode Initiative, the National Human Genome Research Institute (NHGRI)’s CliniSeq®, and the various Genomes2People research projects at Brigham and Health and Harvard Medical School are investigating the use of genome sequencing for apparently healthy individuals. However, there are many scientific and ethical questions about the benefits, harms, and costs of this approach. Here, we explore the opportunities and challenges of utilizing genomic data for predictive, precision, and personalized medicine with several experts in the field.

Please describe your involvement in genomic medicine.

Leslie Biesecker and Eric Green: We are leaders in genetics and genomics research, working at the NHGRI at the NIH for over a quarter century. Our collective research efforts and expertise include both the basic science of genomics [including participation in the Human Genome Project (E.D. Green)] and translational genetics and genomics research (L.G. Biesecker). We are both medically trained: one as a clinical pathologist (E.D. Green) and one as a pediatrician and medical geneticist (L.G. Biesecker). Each of us currently has a major leadership role: one as the Director of NHGRI (E.D. Green) and one as the current President of the American Society of Human Genetics (L.G. Biesecker). From these collective vantage points, we have a broad view of genomics research and the implementation of genomic medicine—a landscape that includes developing technologies, understanding genome structure and function, identifying disease genes, implementing genomic-based clinical tests, and designing precision therapies on the basis of new genetic and genomic knowledge. Having started our medical and research careers before the Human Genome Project, we both find ourselves in awe of the enormous advances in genomics and genetics witnessed in our careers, including those leading to changes in medical practice; these have exceeded what we would have predicted when we first became involved in the field.

Wylie Burke: I am a medical geneticist and academic researcher. My work focuses on the ethical and policy implications of the use of genomics in medicine and public health.

Robert Green: I am a medical geneticist who sees patients and conducts research in preventive genomics. I
What are the risks and benefits of genome/exome sequencing in the individualized testing context, especially as it relates to presumably healthy individuals?

Wylie Burke: Current observations indicate that exome/genome sequencing can sometimes resolve a diagnostic dilemma for patients who have findings that do not allow a specific diagnosis but are suggestive of a genetic disorder. In a public health context (that is, for screening in individuals who are not known to have a genetic disorder), such testing could identify rare individuals with treatable monogenic disorders, such as Lynch syndrome. The risks cannot be fully determined because information about the outcomes of such testing is currently limited and does not involve long-term follow-up. However, it is clear that such testing generates many results of uncertain clinical significance and has the potential to provide misleading information about multifactorial conditions. Studies document inconsistencies in how different laboratories interpret variants, as well as instances of clinically significant variant reclassification. Variant interpretation is more difficult in unselected populations (as opposed to patients with symptoms or a suggestive family history) because we lack population-based data on the natural history and the range of penetrance for most Mendelian conditions. Overall, genome/exome sequencing currently lacks the specificity that is traditionally required for tests used in screening programs. The risks to patients include overdiagnosis, unnecessary medical follow-up, and resulting iatrogenic harm, a “cascade effect” well documented in other areas of medical practice. As a result, the cost to patients and the healthcare system could be substantial. The potential benefits of the use of exome/genome sequencing as a screening tool do not outweigh the considerable potential for risks and costs. Instead, more focused approaches to genomic screening are needed.

Robert Green: It is important when talking about both risks and benefits of sequencing healthy individuals to make distinctions between those that are more and less likely to occur, and to consider the spectrum of risks and benefits alongside other types of testing that we perform in the practice of medicine. The field of genomic medicine has been unnecessarily hampered by “genetic exceptionalism” wherein we have applied one set of rules and standards for genomic testing results and another set for test results in other medical domains. For example, the field of radiology has been dealing with unanticipated findings in indication-based studies for decades and has simply created a series of protocols to guide clinicians within their specialty. Similarly, we screen adults for low-probability events in medicine all the time, because we believe that surveillance and/or orthogonal testing can result in health benefits.

With this in mind, the potential risks of sequencing apparently healthy individuals are largely the same as applying any other risk stratification technologies or screen-
ing biomarkers, i.e., that the information provided to patients and their physicians will lead to overestimation of risk with resulting distress, iatrogenic harm, and unnecessary costs, or that negative results will lead to false reassurance. In addition, like mental health information or human immunodeficiency virus status, genomic information is sensitive and there are risks around data intrusions or the possibilities that such information may be used to discriminate by employers, health insurers, or other types of insurance concerns. Although all of these risks are plausible, and will undoubtedly cause harm to a small percentage of patients, the extent of harm that has been revealed through experimental trials and historical observation suggests that these risks have been vastly overestimated.

The ultimate benefits of genomic sequencing, and ultimately other ‘omics technologies, are no less than the transformation of medicine itself from a reactive enterprise of treating patients who are already ill to a proactive enterprise of preventing illness before it occurs. At this moment, the benefits of “DNA first” testing are that individuals can find out about a variety of monogenic risks for rare heritable conditions, reproductive risks to prevent devastating genetic conditions in their children, variations that can help avoid inappropriate dosing or adverse events with medication use, and even polygenic risks for common conditions. Much has been made about the “actionability” of genetic risks, but our research suggests that this concept is a false flag that artificially simplifies the complexity of how humans utilize information, because varying definitions of medical actionability can incorporate prophylactic surgery, enhanced surveillance, lifestyle changes, and participation in or advocacy for research, and nonmedical actionability can incorporate a host of interpersonal, familial, commercial, and even societal activities. Our research suggests that not only have prior estimates of risk have been exaggerated, but that prior estimates of benefit have been underestimated. When all domains of genomic information are considered and the benefits are amortized over the lifetime of an individual, there is a very high probability that almost everyone will benefit substantially (both medically and nonmedically) from genomic information and that the risks are very low.

**Q&A**

**Leslie Biesecker and Eric Green:** Key to answering the question for healthy individuals is recognizing that over the last decade, the benefits of exome and genome sequencing for individuals with abnormal phenotypes have continuously and relentlessly risen, while the risks have been mostly stable or declined; there is little reason to believe that this trend will change in the foreseeable future. It is now well-established that exome or genome sequencing is the diagnostic test of choice for a number of clinical scenarios, including autism, moderate-to-severe intellectual disability, multiple congenital anomalies, pigmentary retinopathies, and others. The core attribute of exome or genome sequencing is that it provides the clinician a genomics platform for diagnosing a disorder from amongst dozens or even hundreds of alternatives using a single test. There are potential risks associated with exome and genome sequencing (e.g., loss of insurability for life, disability, and long-term care), as is the case for other tests that diagnose a serious medical disorder; other hypothetical risks can be envisioned. But in the end, it will be the increasing benefits of exome and genome sequencing that will tip the benefit-vs-risk calculation in favor of the former.

Although reducing risk is always desirable, many routine medical treatments (e.g., surgery and chemotherapy) are associated with inherent risks, but we use these treatments because the benefits are high. As the benefits of genomic medicine increase, the small but real risks will become less concerning; as a field, we need to focus on identifying and explaining the benefits, but not insist that the risks be driven to zero.

The risk-benefit ratio associated with exome or genome sequencing is different for the healthy individual. The risks are the same as those described above for the patient with one of the currently accepted indications for genomic testing, but the benefits are more modest. At present, the large majority of healthy individuals do not receive substantial benefit from exome or genome sequencing; however, this is likely to change as ongoing research projects establish the opportunities (and limitations) of using genomic information to identify disease risk in individuals before they are overtly ill.

**How can a clinician decide if genome/exome analysis is the right test for their patient, especially in the context of presumably healthy individuals?**

**Robert Green:** Indication-based genome/exome sequencing is clearly indicated, within existing standards of care, for patient with symptoms for which a hereditary condition or molecular etiology is suspected but the clinical presentation does not permit narrowing of gene candidates to a specific panel. Reimbursement for this sort of diagnostic testing is increasingly covered by medical insurers.

At this moment, proactive or predispositional sequencing of apparently healthy individuals is not standard of care, and this fact should be made clear to all patients who are interested. Moreover, despite our contention that there is long-term medical value for many patients and their providers in learning such information, this has not been fully demonstrated and there is limited reimbursement for most preventive screening practices with less than definitive data for medical benefit, particularly when the benefit may accrue years or decades after
the testing. Thus, clinicians must help patients decide whether out-of-pocket costs are worthwhile for that particular patient. The potential for genomic testing purchased by patients who can afford such payments along with the inability of other patients to pay for these tests presents a challenge to societal values and threats to create an economic (and ethnic) “genomic divide” between those with resources to spend on elective genomics and those without such resources.

Despite the absence of definitive evidence for benefit and cost-effectiveness in genome sequencing of healthy individuals, costs will continue to come down and interest in such testing will undoubtedly grow. Clinical research studies could be designed that would provide such evidence, but well-controlled research studies of the size and duration that would generate evidence to the satisfaction of expert bodies like the US Preventive Services Task Force are not currently being funded by research. Even the All of Us Research Project, with its ambitious goals for recruitment and diversity and its commitment to returning genomic information that might be medically important to participants, is not designed to rigorously assess the benefits and harms of multidomain genetic sequencing. With demand and access increasing, and with definitive evidence still far off, clinicians should (a) alert healthy patients that genomic sequencing is not standard of care, (b) standardize some form of clinical consent that alerts patients to possible findings and the downstream risks, (c) contextualize the entire process by integrating the patient's prior medical and family history, (d) be prepared to follow up on genomic risk variants that are identified with appropriate referrals, and (e) advocate for the “service with evidence collection” model by encouraging patients to enroll in research studies like the PeopleSeq Consortium, in which they can self-report on their medical, behavioral, and economic outcomes.

Leslie Biesecker and Eric Green: As the overall risk-benefit ratio associated with exome or genome sequencing is not yet convincingly favorable for apparently healthy individuals, we can ask if there are subsets of healthy individuals for whom such genomic testing would be appropriate. We have gained considerable insight about this question from our ClinSeq® study, which has shown that there are substantial numbers of technologically and medically sophisticated individuals who are responsibly curious about their genomes, have favorable attitudes about accepting risk and living with uncertainty, and want to be participants at the cutting edge of medicine, science, and technology. For these healthy individuals, genome sequencing is a perfectly reasonable option, and we should not discourage such individuals but instead learn from them. Sequencing the genomes of apparently healthy individuals can be done safely in clinical research studies and in a learning health-care environment. Recognizing that such motivated, healthy individuals will often be well-educated and affluent, we should be mindful about generalizing their experiences to all parts of society. Nonetheless, learning from such early adopters will inform decisions about the widespread implementation of genomic medicine, helping to ensure that everyone benefits from genomics.

Wylie Burke: The evidence we now have argues for limiting genome/exome analysis to patients presenting with diagnostic dilemmas for which a genetic cause is suspected. Current evidence also argues against the use of exome/genome sequencing as a screening tool because of the potential for ambiguous or misleading information, iatrogenic harm, and unwarranted costs to patients and the healthcare system. However, there is certainly promise for targeted genomic screening in future medical care. With appropriate population-based research, we can anticipate the ability to define a limited genomic screen focused on analysis of a subset of well-understood genes with variants leading to medically actionable conditions. A few genes are close to this threshold—e.g., BRCA1\(^9\), BRCA2, HFE and genes associated with Lynch Syndrome. Genomic screening for pharmacogenetic variants is also likely to hold value in the future, as more information about the clinical utility of such variants is produced. But assuring benefit and reducing harm will require a disciplined approach in which analysis and reporting is limited to genes that can provide reliable screening information.

Have any results from genome sequencing projects been surprising to you? If so, please describe.

Leslie Biesecker and Eric Green: Recent genomic studies have shown that nearly half of the patients with some form of early onset cancer, but who lack a family history of cancer, actually have a familial cancer syndrome. A similar situation is seen with some sex-limited cancers (e.g., breast and ovarian cancer); for example, if a woman happens to be from a family in which there are more males than females, the inheritance of a pathogenic genomic variant may not be recognized, leading to unnecessary delays in diagnosis. Although these examples should not have surprised us, they do illustrate the need to break out of our old ways of thinking. Because single-gene testing was so inefficient and expensive, our general approach was that a family history had to include multiple individuals with cancer to justify genomic testing in search of a familial cancer syndrome. This was an artifact

\(^9\) Human genes: BRCA1, BRCA1 DNA repair associated; BRCA2, BRCA2 DNA repair associated; HFE, homeostatic iron regulator.
of our (then) limited testing abilities. We have to change our thinking toward the goal of diagnosing the first person in a family with familial cancer rather than the fifth or sixth.

**Wylie Burke:** The willingness of some experts to recommend exome/genome sequencing of healthy people for the purposes of screening, in the face of scant evidence for benefits and substantial evidence of ambiguous and uncertain findings, has been surprising.

**Robert Green:** The first area that surprised us, and I think the entire field of genetics, is how many people want genetic information, including genetic risk information, and for those who want to learn such information, how remarkably safe such disclosures have been. Even today there are repeated concerns about injecting “anxiety” into people’s lives when they receive genetic risk information, yet our early studies on the return of genetic risk information for Alzheimer disease, our analyses of customers receiving direct-to-consumer risk information, and our subsequent trials of comprehensive sequencing among adult patients and parents of newborns are all completely consistent. In fact, these studies all show that there is very little distress that occurs when healthy individuals (or the parents of healthy infants) request and receive genetic risk information. There certainly are examples of significant distress and even regret among persons who learn about their genetic risks, as there would be for anyone learning about increased medical risk from any source, but by and large the question of widespread anxiety, depression, or distress among people receiving genetic risk information, even for the most horrific and untreatable of conditions, has been asked and resoundingly answered. It is not at all common!

Another area of surprise has been the frequency of monogenic findings in the MedSeq and BabySeq Projects. The professional identities of most medical geneticists have been built around the notion that they are specialists in monogenic conditions that only impact the health of a small fraction of children, whose medical problems are often devastatingly obvious in the newborn period or early childhood. Considering the possibility that monogenic diseases are, over time, common contributors to pediatric and adult morbidity is a startling re-framing of these assumptions.

A third area that I find surprising is the recent rehabilitation and enthusiasm for polygenic risk scores (PRSs). Such scores were presented in consumer-facing genetic testing companies over a decade ago and widely criticized as irrelevant to health. PRSs have now been recharacterized with more computational sophistication and more confirmatory validation by the academic community, with an acknowledgment that those in the highest segment of the risk distribution curves do, in fact, have clinically meaningful risk, although many questions about how to apply such information, particularly across ancestry categories, remain to be solved.

**Many have been critical about the cost of genomic medicine as compared to the actual reaping of benefits. What are your thoughts on this topic?**

**Wylie Burke:** The overall costs of genome analysis outweigh the benefits for most patients and will continue to do so even after variant interpretation becomes more reliable. The costs include the financial resources needed for testing, interpretation, and medical follow-up to clarify ambiguous findings. They also include the time required of physicians and patients for discussion of ambiguous findings, unnecessary work-ups, the risk of iatrogenic harm, and, most significantly, the opportunity cost involved in using health resources for genome/exome sequencing that could otherwise be used for proven preventive interventions and community-based efforts to promote healthy social environments.

**Leslie Biesecker and Eric Green:** The costs of exome and genome sequencing are now comparable to those associated with a number of tests that are commonly used in clinical practice. Although some might regard such costs as still relatively high, it is the cost per diagnosis that should be considered the key metric. As noted above, sequence-based genomic tests have higher diagnostic yields than many other medical tests. The focus should really be on the cost per diagnosis and the value of ending what has been termed the “diagnostic odyssey.” Consideration should also be given to the metric used for all other medical practices, which would involve comparing the cost of quality-adjusted life years associated with genomic testing vs current testing modalities. The research to understand the economics of genomic medicine is still at a very early stage, but there are reasons to be optimistic that the numbers will be favorable in many clinical situations and, eventually, in healthy individuals.

**Robert Green:** In my view, this is a very short-sighted argument because the cost of both sequencing and interpretation have fallen so dramatically over recent years and there is every indication that they will continue to fall further. Many, including the CEO of Illumina, have predicted that we will soon enter a phase in which genomes will be sequenced for $100, and others have suggested that such technology will be provided freely as promotional gifts by companies providing products or services, or by health systems evolving toward accountable care that come to realize how much disease could be prevented by such implementation.

With so much emphasis on the plunging costs of the sequencing itself, even experts tend to forget that the
medical value of the sequence depends upon how extensively and how accurately it is interpreted. Even with the same underlying technology for sequencing, there is a very different value proposition to interpret 59 genes vs 200 genes vs 2000 genes! Here costs could stabilize or even increase as patients and providers realize the extensive value of interpreting larger and larger panels, of using algorithms that accurately detect and classify structural variations, and of getting input from sophisticated molecular geneticists who can manually scour the scientific literature to make the most accurate judgments about disease-gene correlation and variant pathogenicity. In our MedSeq and BabySeq Projects, we experimented with “comprehensive” best-in-class interpretations beginning with over 4000 genes that had strong evidence for disease-gene associations. From this starting point, we found that over 20% of healthy adults had monogenic disease risks, over 90% carried variants for recessive conditions, and over 80% carried markers for atypical responses to at least 1 category of medications. But generating these interpretations to the highest possible standards was labor intensive, translating into thousands of dollars of interpretive effort per genome. As the technical costs of generating the sequences become increasingly commodified, it will be the breadth and skill of interpretation that will distinguish the quality of leading laboratories and clinical teams of the future.

What are your thoughts on using genomics to guide risk for common disease, for example with PRSs or other genetic markers of disease?

Robert Green: As noted above, there has been a recent reexamination of the potential value of PRSs for identifying individuals who are at higher risk for common diseases such as coronary artery disease, type II diabetes, atrial fibrillation, depression, and many others. On the one hand, this is a much needed corrective for the blanket condemnations of this approach over the past decade. It has always been clear that some individuals in the top percentiles of polygenic risk might benefit from identification. On the other hand, PRSs should be validly generated for different ancestry groups, the effect sizes of the top percentiles at risk should be clearly understood, and the benefits of applying such scores should be evaluated in controlled trials before such risk stratification is broadly implemented.

It is tempting to design studies asking whether providers will do something—or anything—when confronted with PRSs, but this line of reasoning is flawed. If you give a provider a report saying patient X has increased risk of cardiovascular disease and recommend that the provider add a test or change a medication, you are simply measuring whether providers follow directions, not the efficacy of PRSs. The more interesting question is whether providers can integrate PRSs into their own decisional matrices to more aggressively encourage patients to follow existing best practices, and whether this results in better health outcomes, or at least better proxy phenotypes for health outcomes. We did just this in the first randomized pragmatic trial of a PRS for coronary artery disease, led by Iftikar Kullo and published in 2016, in which we demonstrated that patients whose clinicians were apprised of their high PRSs had significantly lowered lipid measures.

The issues around implementing PRSs are quite similar to those already discussed in implementing monogenic risk variants—misunderstanding by patients and providers, inadequate evidence of clinical utility, and the possibility of false reassurance. Indeed, the distinction between persons at increased risk for common complex diseases on the basis of thousands or even millions of markers and persons who have a pathogenic variant for a monogenic condition for which penetrance and expressivity are shaped by epistasis from an unknown number of other genes is somewhat artificial. In the end there are only a few purely deterministic genetic markers and everything else is, to a greater or lesser degree, “polygenic.”

Wylie Burke: This proposal assumes a greater predictive value than genetic information can provide and discounts the importance of risk factors unrelated to genetics. Identifying patients at increased risk for common complex diseases is already easy to do—often with effective biomarkers, such as glycohemoglobin (Hb A1C), lipid concentrations, and blood pressure, in combination with routine family history information. More to the point, risk factors unrelated to genetics, such as smoking, diet, and sedentary lifestyle—as well as social determinants such as exposure to poverty, food insecurity, violence, and discrimination—are critical determinants of health risk. The challenge lies not in risk identification but, rather, in creating healthier social environments and assisting patients to pursue healthier lifestyles. Genetic risk information is not motivating for most patients—nor is nongenetic risk information. Instead, patients need interventions oriented to their social circumstances that reduce barriers to lifestyle change.

Leslie Biesecker and Eric Green: The clinical use of PRSs is in its infancy, but there seems to be some exciting promise on the basis of studies to date. It is likely that some risk scores will be shown to be comparable to the relative risks of having a pathogenic genomic variant for a single-gene disorder, making them clinically valuable. As the anticipated advances in this area are realized, it will be critically important that validated risk scores are estab-
lished across heterogeneous ancestral populations to ensure that such scores are accurate for individual patients and appropriate for use with all population groups, so as not to exacerbate health disparities.

** Genome sequencing of presumably healthy newborns has been criticized because of its potential to limit a child’s right to an open future. What are your thoughts on the benefits of newborn genome sequencing in this context and how to address this criticism?**

**Leslie Biesecker and Eric Green:** This is an interesting hypothetical risk of genomics, but the question again gets to risks vs benefits. Parents make difficult choices for sick children every day, and some of those choices limit the future options that the child may have. When the benefits of a test are high, they outweigh a theoretical harm (e.g., a small risk related to “limiting an open future”). In situations like this, the most important value to preserve is trusting that parents will make the best decisions for their children when presented with appropriate medical alternatives.

**Robert Green:** First, we should take pains to differentiate the use of elective sequencing by the parents of healthy newborn infants who are motivated to protect the future health of their children and the state-mandated system of newborn screening (NBS) that is currently in place with the US and across much of the world.

As with adults, elective sequencing of healthy children is not standard of care, but if evidence supports sequencing adults for predictive and preventive purposes, then it is only logical that preventive strategies could be applied earlier if risks were recognized in childhood. Just imagine that you are a pediatrician and ask yourself, “when would you would prefer to learn that an individual had familial hypercholesterolemia, adenomatous polyposis, a tendency toward aortic aneurysm, or a life-threatening reaction to carbamazepine?” Wouldn’t earlier be better than later? The traditions of clinical medicine, with its joint decision-making and personalized judgements, offer enormous and legitimate flexibility for discussion and action between provider and parents in the office setting. If parents would like their healthy newborns to be sequenced in a medical context that provides appropriate information and expertise, I believe there is sufficient evidence of minimal harm and potential benefit from our BabySeq Project to support this.

By contrast, the current state-mandated NBS is a public health program that requires newborn infants to undergo biochemical screening for conditions for which time to recognition and intervention are critical. NBS is considered a cost-effective public health success, despite the controversial facts that NBS laboratories screen for genetic diseases and indefinitely store the DNA of virtually every infant in the country. Because NBS programs have no enforcement capabilities, they have remained viable by keeping a relatively low public profile and by adding new assays through a careful, incremental “behind the scenes” process. Preparing state laboratories to add universal multi-panel sequencing tests as a primary screen will, for some time, be prohibitively expensive and would be inappropriate for a mandated program without a much higher evidentiary bar for cost-effectiveness and clear health benefit. Unfortunately, even public discussion of adding genomic sequencing to the state-mandated newborn testing regimen might be disruptive because it could raise public awareness around current storage of blood spots and inflame privacy zealots to destructively confront state laboratory practices, as was done in Michigan and Texas, threatening the foundation of the already existing NBS program.

Nonetheless, as the President’s Council on Bioethics concluded as early as 2008, it may “...prove impossible to hinder the logic of genomic medicine from assimilating the currently limited practice of newborn screening into its all-embracing paradigm.” This eventual collision between NBS and genomic medicine can only be managed through transparency and through social advocacy that de-exceptionalizes genomics and grounds both benefits and harms within the same values we pursue for the rest of medicine. The child’s “right to an open future” is a sentiment left over from a time when genomic risk information was considered to be psychologically dangerous and genomic risk was seen as far more deterministic and less actionable than we now know it to be. Just as parents take responsibility for a child’s future in every other medical and nonmedical domain, so should they be free to take responsibility for learning about a child’s genetic risk for child-onset, or even the child’s adult-onset, genetic conditions.

**Wylie Burke:** NBS has the goal of identifying actionable medical conditions that require treatment in the newborn or early childhood period. To the extent that sequencing information can contribute to this goal, it should be considered. Health information beyond this goal is not appropriate or helpful to newborns and could be harmful, for the same reasons that exome/gene sequencing is potentially harmful for healthy adults when used as a screening tool. The use of genome sequencing for NBS should be limited to genes associated with serious, actionable conditions with onset in early childhood.

**Although an individual’s genome sequence is timeless, the interpretation of the sequencing data is not. Describe the challenges and progresses with regards to**
genomic data reinterpretation and reintegration in the medical record when new discoveries are made.

Wylie Burke: Variant interpretation involves uncertainty and error. When genomic tests are used, clinicians and laboratories assume a responsibility to take reasonable measures to plan for reinterpretation and inform patients of any variant reclassification that occurs. The scope of this responsibility, both legal and ethical, is still being debated, and methods to assure timely reinterpretation and patient notification are still being developed. This aspect of genome sequencing is a major challenge and adds to the argument for limiting exome/genome sequencing to uses focused on diagnostic dilemmas, until the evidence base and techniques for variant interpretation improve.

Robert Green: Genomic sequences are not quite timeless, in that technical advances in both identification of nucleotides within the individual reads and the algorithms used to correctly call both single-nucleotide polymorphisms (SNPs) and copy-number variations from the reads are constantly improving. But there is no question that knowledge at both the gene and variant level is rapidly progressing. The question of how much changes in the interpretation of genome over time has been the subject of much debate, and in our recently published reanalysis of MedSeq Project genomes led by Kalotina Machini and Heidi Rehm, we demonstrated that after only a 1–2 year interval, 22% of the reports had updates or changes in variant interpretations. This proportion of changing reports highlights the need for specific policies around reanalysis and eventually reimbursement for reanalysis of genomes that are being used in medicine to make interpretation as current and accurate as possible. This is an important feature to apply to indication-based sequencing, but, ironically, it is even more important in elective sequencing because healthy individuals may bring medical surveillance to bear over decades to a pathogenic risk variant, and if that variant were reclassified, particularly as more benign than originally thought, then the patient could abandon that surveillance.

Genomic information obviously needs to be integrated with the electronic health record (EHR), but most laboratories are still attempting to send original reports through noninteractive PDFs that may not even be seen by a provider. In addition, several vendors have successfully integrated EHR alerts when prior variants are reclassified, but providers are routinely bombarded with so many alerts that it is questionable whether this mechanism can be effective. Fortunately, there are many commercial and academic groups seeking to integrate a true dashboard of genomic information into the EHR along with just-in-time, point-of-care decision support, particularly for pharmacogenomic variants when specific medications are being prescribed.

Leslie Bieseker and Eric Green: The implementation of genomic medicine must include routines that properly compensate professionals for their efforts to improve the health of their patients. A key part of this will be to ensure that long-term clinical service obligations in genomics are economically incentivized to favor the desired outcomes, such as the reinterpretation of a patient’s genome sequence. This is a nascent challenge for genomic medicine, but one that both does not seem insurmountable and does not need to be solved immediately. To harbor a vision of rational healthcare economics is not irrational.

**What progress has been made and what obstacles need to be overcome to more fully utilize genome sequencing data for precision and predictive medicine?**

Robert Green: Tremendous progress has been made in lowering the cost and increasing the speed and accuracy of identifying SNPs, indels, and structural variations in genomic sequencing. Large-scale collections of genomic data without specific phenotypes, such as ExAC and gnomAD, have offered insight into ancestry-specific variant frequencies that have improved the interpretation of variants in patients with non-European ancestry, but much more needs to be done. Collecting variants into databases like ClinVar with expert panels to assess the existing evidence for pathogenicity is critical, but that evidence is fundamentally constrained by the absence of careful phenotyping and long-term clinical follow-up among healthy persons carrying variants. To fully take advantage of the genetic risk information in the genome of an apparently healthy person, it is necessary to (a) sequence and interpret a large number of disease-associated genes and (b) use the genetic information to specifically search for previously unrecognized mild and intermediate phenotypes across the longest time window possible.

We have published early data from an extremely large panel of several thousand disease-associated genes in the MedSeq and BabySeq Projects, and these analyses that suggest 11%–20% of healthy individuals may carry monogenic risk variants for dominant or (biallelic) recessive conditions. Targeted re-phenotyping of these individuals has further suggested that a substantial proportion of these, perhaps as many as 25%, may already be manifesting clinical features of the previously unnoticed or unrecognized genetic condition. In separate studies, we have found that when individuals with monogenic risk variants are followed for an average of over 20 years in the Framingham Heart Study, a high proportion of them develop the condition heralded within their DNA, suggesting that penetrance over time may be largely underestimated. Taken together, these data suggest that many...
more people than previously suspected may be at risk, and eventually clinically affected, by monogenic genetic conditions. Monogenic diseases have the reputation of being individually rare but in the aggregate may be far more common, and clinically impactful, than previously suspected.

The largest deficit in the evidence base needed for the full application of genomic medicine in apparently healthy people is well-controlled, long-term outcomes studies in which deep phenotyping after genomic testing can be performed and medical benefits and harms can be tracked. The use of genomic information for risk stratification is a potentially transformational medical intervention and, like any important intervention, should be thoroughly vetted for benefits, harms and costs. Some of the small-scale NIH-funded projects within the CSER (Clinical Sequencing Evidence-Generating Research) and IGNITE (Implementing Genomics in Practice) consortia are exploring these themes, but none of the large-scale, NIH-supported consortia such as eMERGE (Electronic Medical Records and Genomics) or All of Us are yet collecting these data in a rigorous or controlled manner.

Wylie Burke: Genomics will always have a limited role in precision and predictive medicine. Precision medicine has the goal of using information about a person’s genetics, environment, and lifestyle to individualize care. For most patients, this goal is realized primarily by information unrelated to genomics, such as information about the patient’s preferences and goals, diet, activity level, smoking status, socioeconomic circumstances, and phenotypic measures like cholesterol, Hb A1c, and blood pressure.

Leslie Biesecker and Eric Green: Although exome and genome sequencing has now matured to the point of being an appropriate and effective clinical diagnostic tool, additional improvements are still needed for its widespread use with healthy individuals. The diagnostic and screening yields for many clinical conditions can be increased by improving our ability to infer the clinical relevance of genomic variants, derive data from difficult-to-sequence genomic regions, and understand noncoding variants, among other challenges. Key to improving our understanding of genomic variants will be refining and standardizing guidelines for variant interpretation and increasing the sharing of clinical and genomic data. These are central activities of the Clinical Genome (ClinGen) Resource, which has led to the public deposition of more than 500,000 genomic variants in ClinVar. The public availability of such standardized data recently led the US Food and Drug Administration to endorse ClinGen as the first regulatory-grade human genomic variant database, which will now accelerate progress in genomic medicine.

A major obstacle to further progress is changing the mindset of practitioners so that they recognize that exome and genome sequencing is now in the mainstream of medicine. Genetic and genomic tests have a history of being considered arcane tools for use by a few, highly specialized providers. But exome and genome sequencing is emerging as a tool that any clinician can use in caring for their patients. Indeed, we believe that such genomic testing can improve access to specialized healthcare services, especially for those who live large distances from tertiary care centers. Instead of rural patients traveling hours each time to visit one in a chain of many providers, what if the local family practitioner had the patient’s blood shipped for exome or genome sequencing, with the results indicating the most appropriate specialist to then travel to see? By bringing technology to the patient instead of journeying the patient from one specialist to another, healthcare disparities could be reduced. This points to the need to dispense with some old presumptions about high-technology medicine—specifically, these new sequencing-based genomic tests can be used by many doctors in many settings to bring genomic medicine to many patients.

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