Decision-Making in the Age of Whole Genome Sequencing

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Introduction

In 2001, the first human genome sequence was produced: it took 15 years and $3 billion (Lander et al. 2001; Venter et al. 2001; International Human Genome Sequencing Consortium 2004). Today, an entire human genome can be sequenced for less than $5000 (Drmanac et al. 2010). The cost of whole genome sequencing (WGS) is falling at a super Moore's law rate (National Research Council 2011). Technologies on the horizon like the IBM DNA transistor have theoretical sequencing limits in the hundreds of millions of bases per second per transistor. Packing millions of such transistors together in a single chip or handheld device could produce terabase and even petabase scale sequencing in seconds (Schadt et al. 2010). There seems to be little doubt that WGS could be routinely available to patients for a few dollars within the next 10 years.

Today, patients can obtain personal results from WGS, or "personal genome sequencing," in research studies like the MedSeq Project (www.genomes2people.org/g2p) and the Personal Genome Project (Church 2005; Lunshof et al. 2008; Angrist 2009; Lunshof et al. 2010). Consumers have obtained whole exome sequencing (WES) from direct-to-consumer (DTC) company 23andMe (http://blog.23andme.com/23andme-research/23andme-moves-into-the-world-of-sequencing/), and Illumina's "MyGenome" app allows healthcare providers access to personal WGS results (www.illumina.com/company/events/understand-your-genome.html).

The rate of technological development has outpaced our ability to fully address important questions relating not only to the health, social, and economic implications of having easy access to one's genome, but also regarding patient education, understanding, and informed decision-making (Green and Guyer 2011; Brunham and Hayden 2012). Deciding whether to have personal WGS is complex, and involves considering scientific uncertainty, weighing up potential benefits and risks, understanding the range of possible results that could arise, and how such results may be used or interpreted by others (Green and Guyer 2011).

In clinical genetics, the gold standard for ensuring patients make informed decisions about genetic testing is in-person genetic counseling with a trained genetic counselor. The 2006 National Society of Genetic Counselors (NSGC) definition of genetic counseling is that genetic counseling "is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This

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process integrates … interpretation of family and medical histories to assess the chance of disease occurrence or recurrence; education about inheritance, testing, management, prevention, resources and research; and counseling to promote informed choices and adaptation to the risk or condition" (Walker 2009, p. 7).

However, genetic counseling services are already stretched (Brunham and Hayden 2012). There are currently just over 4000 Board Certified Genetic Counselors and 33 Accredited Graduate Programs in Genetic Counseling in the US (http://www.abgc.net/About_ABGC/GeneticCounselors.asp; accessed 13 June 2016), yet hundreds of thousands of genomes are being sequenced presently and that number is growing at an exponential pace (while the training of genetic counselors is steady or at best growing at a linear pace). It would therefore be physically impossible for everyone getting sequenced to have even 5 min of time with a genetic counselor, let alone the hour or two it routinely takes to fully educate and counsel patients considering genetic testing at the present time.

Most DTC personal genomics companies provide little to no in-person genetic counseling (Dohany et al. 2012). For example, individuals purchasing personal genomics products from the DTC genetic testing company 23andme (www.23andme.com) are not required to have genetic counseling before, during, or after their purchase. Of note, Navigenics (www.navigenics.com), the one well-known DTC genetic testing company providing genetic information within a more traditional genetic counseling model, was bought by Life Technologies in 2012 (www.bloomberg.com/news/articles/2012-07-16/life-technologies-buys-navigenics-for-genetic-diagnostics; accessed 13 June 2016), supporting the suggestion that this is arguably not a sustainable model. It is vital that questions around the extent to which genetic counseling is a critical part of the genetic testing process, and whether novel educational and support systems can replace or enhance in-personal genetic counseling, are addressed.

In this chapter, we discuss how decision-making about genome sequencing may differ from decision-making about past health-related tests, review the limited evidence at present on decision-making about genome sequencing, discuss how the rate of evidence is growing exponentially and so decision-making is a moving target that we can expect to be constantly changing and very dynamic for the foreseeable future, and discuss the challenges and future directions for the field. We focus primarily on WGS in the context of "healthy" individuals, that is, individuals not selected specifically for having an initial disease or phenotype of interest. Although much of WGS being done today is, for example, to uncover the cause of an undiagnosed disease or to try to help treat a patient diagnosed with cancer, we anticipate that within the next few years WGS will not be restricted to individuals and families affected with rare genetic disorders and diseases, but that rather we are moving toward a future where every individual across society will have their genome sequenced. Relatedly, genomics research studies are growing in size and scope at a rapid pace. The evidence-based, double-blind randomized clinical trial paradigm is not adequate to handle all of the information coming and we therefore need a different paradigm, one that considers patient populations to be clinical trial populations, where medical evidence is built up in real time, with decision-making happening within adaptive designs that are constantly being updated as new data and results emerge. Patients and research participants will be required to make decisions about having WGS done and receiving results from it, acknowledging that the context in which they are having it done is constantly changing and evolving, and that therefore all of the future outcomes of the research or clinical procedures cannot be predicted at baseline. For the purposes of this chapter, we consider "healthy" individuals to include both research participants and future "healthy" "patients," given the lines between these two groups are arguably blurred.

Genome Sequencing and "Big Data"

From a data perspective and the impact of data on our daily lives, life was much simpler 30 years ago. Few computerized systems existed

to store your personal information, the Internet was so primitive that most were not even aware it existed, handheld cellular phones were owned by only a privileged few thousand individuals, and DNA sequencing was carried out by running DNA out on gels. However, today we find ourselves in the midst of a big data revolution, a revolution permeating nearly every aspect of our lives. Electronic devices that consume much of our attention on a daily basis enable rapid transactions among individuals and between individuals and entire communities on unprecedented scales, where all of the information involved in these daily transactions can be seamlessly stored in digital form, whether the transactions involve cell phone calls, text messages, credit card purchases, emails, or visits to the doctor's office in which all tests carried out are digitized and entered into your electronic medical record.

The life and biomedical sciences have not stood on the sidelines of this revolution. There has been an incredible wave of new technologies in genomics—such as next-generation sequencing technologies (Eid et al. 2009), sophisticated imaging systems, and mass spectrometry-based flow cytometry (Bandura et al. 2009)—enabling data to be generated at very large scales. As a result we can monitor the expression of tens of thousands of protein- and noncoding genes simultaneously (Emilsson et al. 2008; Chen et al. 2012), score hundreds of thousands of Single-Nucleotide Polymorphisms (SNPs) in individual samples (Altshuler et al. 2008), sequence entire human genomes now for less than $5000 (Drmanac et al. 2010), and relate all of these data patterns to a great diversity of other biologically relevant information (clinical data, biochemical data, social networking data, etc.). Given technologies on the horizon like the IBM DNA transistor with theoretical sequencing limits in the hundreds of millions of bases per second per transistor (imagine millions of these transistors packed together in a single handheld device) (Schadt et al. 2010), we would not be talking in the future about Google rolling through neighborhoods with Wi-Fi sniffing equipment (Kravets 2010), but rather we would be talking about DNA sniffing equipment rolling through neighborhoods sequencing everything they encounter in real time and then pumping such data into big data clouds to link with all other available information in the digital universe.

Keeping pace with these life sciences technology advances are information technology advances in which now more "classic" information-savvy companies like Microsoft, Amazon, Google, Facebook, Ebay, and Yahoo as well as a new breed of emerging big data mining companies such as Recorded Future, Factual, Locu, and Palantir have led the way in becoming masters of petabyte- and exabyte-scale datasets—linking pieces of data distributed over massively parallel architectures in response to user requests and presenting results to the user in a matter of seconds. Following these advances made in other disciplines, we are on track to access the same types of tools to tackle the big data problems now being faced by the life and biomedical sciences, especially as it relates to the interpretation of personal genomes, better informing a human genome by taking into account the digital universe of information, as opposed to the information that can be stored in the brain of a medical geneticist or genetic counselor. But large-scale data generation and big computer infrastructures are just two legs of the stool regarding what is needed to revolutionize our understanding of our own DNA. While the data revolution is driven by technologies that provide insights into how living systems operate, enabling decision-making at a hierarchy of levels (patients, physicians, expert researchers, physician scientists, big data mining firms, marketing firms, and lay individuals who simply want to better understand themselves), achieving understanding from such data that drives the most informed decisions will require that we tame the burgeoning information these technologies generate.

If we want to achieve understanding from the big genomics data, organize it, compute on it, build predictive models from it, then we must employ statistical reasoning beyond the more classic hypothesis testing of yesteryear. We have moved well beyond the idea that we can simply repeat experiments to validate findings generated in populations. While first instances of the

Central Dogma of Biology were incredibly simple, today, given the complex interplay of multiple dimensions of data (DNA, RNA, protein, metabolite, cellular, physiologic, ecologic and social structures more generally), a much more holistic view must be taken in which we embrace complexity in its entirety. Our emerging view of complex biological systems is one of a dynamic, fluid system that is able to reconfigure itself as conditions demand (Zerhouni 2003; Barabasi and Oltvai 2004; Han et al. 2004; Luscombe et al. 2004; Pinto et al. 2004).

Soon average individuals will have access to detailed information about their genetic makeup, the molecular states of different cell types and tissues sampled from their bodies, and more detailed, longitudinal collections of phenotypes informing on their weight, blood pressure, glucose and insulin levels, and a myriad of other clinical traits that inform on disease, disease risk, and drug response. Decisions motivated by interpretations of this information will be maximally informed if the right types of data are appropriately integrated and presented to us or our doctors in ways that maximize chances of assessing disease risk, detecting disease, or developing treatment strategies tailored to our particular disease subtype and individual genetic/environmental backgrounds. Already, there are powerful examples of how this new era of personalized medicine will change the way we are diagnosed and treated. A routine genetic test can indicate whether breast cancer patients will respond to treatment with Herceptin, and testing for certain changes in DNA that affect a gene needed to convert vitamin K into an active form required for proper blood clotting is being shown to assist doctors in assessing whether patients requiring an anticoagulant can tolerate a high dose of warfarin or whether a lower dose should be given to prevent what could be fatal side effects.

Just like the security analysts sifting through mountains of data to identify the next big threat, individuals concerned about their well-being, doctors who seek to treat these individuals, and researchers searching for causes and treatments of disease, will face their own "big data problem" as evolving technologies enable unprecedented, comprehensive views of our bodies at the genetic, molecular, and physiological levels. While many of us have grown up in the era of doctors wielding stethoscopes and thermometers as their primary tools to rapidly assess a patient's state of health, tomorrow's doctors will be faced with a myriad of "biological chips" and imaging technologies capable of monitoring variations in our DNA, variations in the activities of genes and proteins in our bodies that drive all cellular functions, and providing for resolution at the single-cell level of any organ in our bodies. There is a need to master the large-scale molecular data that underlies pathophysiological states, employ sophisticated mathematical algorithms capable of data integration, and leverage appropriate informatics infrastructure to apply these algorithms and translate the results into manageable bites of information that can be consumed by physicians and patients, if we hope to realize the dream of personalized medicine. Ultimately, through the use of advanced biomedical and informatics technologies, we will be able to enable different users of genomic information to become masters of this information.

How Does Decision-Making About Genome Sequencing Differ from Decision-Making About Other Health-Related Technologies?

The Changing Landscape of Actionable Variation in Genome-Wide Sequencing Data

The interpretation of genome-wide sequencing data to date has largely focused on variants that lead to changes in protein coding sequence. On average, comparing a given individual's genome assembled from WGS data to a common reference sequence will result in the identification of three to four million small nucleotide sequence variants, 30,000–50,000 of which will fall within the protein coding part of genes (Biesecker 2012, p. 394). While perhaps a majority of these protein coding variants will not be of clinical

significance or of importance to the individual, many of these variants will be of clinical or personal significance, with current estimates demonstrating that most individuals who have been sequenced harbor three to eight actionable variants (Speicher et al. 2010; c. f. Biesecker 2012). While these protein coding variants may seem large in volume, these investigations to date have not paid significant attention to the vast number of variants that fall outside of gene regions (the case for the vast number of variants, including those associated with disease) nor is the sequence data generated today able to comprehensively characterize structural variations given the short-read nature of next-generation sequencing (NGS) technologies. Existing studies of gene expression data have associated many thousands of sequence variants with the expression levels of genes, and these variants have also been shown to be enriched for disease-associated alleles from the genome-wide association studies (GWAS). Layer on top of the work coming out of the ENCODE project in which roughly 80 % of the genome has been shown to be actively bound by proteins in tissue and development specific ways (Bernstein et al. 2012), and the expectation is that the vast majority of variants that are either actionable on their own or comprising multivariate models that well predict phenotypes of interest, will be regulatory in nature. Thus, the sheer volume of data produced by WGS is unprecedented, and the types of results that an individual may receive through WGS are unpredictable and open-ended. This has important implications for decision-making about WGS that are discussed further below.

Unpredictability of Diseases/Traits for Which Information May Be Uncovered

Individuals making decisions about having WGS done are not making a decision about receiving information about one disease or trait, but rather about whether to receive information about an undefined, unpredictable number and types of diseases and traits. This therefore differs from most other types of decision-making in the health arena, which tend to be disease-specific. For example, factors influencing a man's decision about whether to go ahead with prostate-specific androgen (PSA) testing for prostate cancer risk may include his perceived or actual risk of developing the disease, his family history of the disease, and his fear of the disease, as well as his perceptions or understandings of the benefits versus limitations of the test itself. The man in this scenario may weigh up how he would feel in response to receiving high risk results for prostate cancer based on PSA testing, and what he would do with this information about his prostate cancer risk. Similarly, a woman making a decision about *BRCA1/2* genetic testing for breast cancer risk, may factor in her personal and family history of breast cancer, her feelings about breast cancer, how a positive or negative *BRCA1/2* test result would make her feel, and what she would do with that result. In contrast, an individual considering how he or she might feel in response to results from WGS, has to consider how they would feel getting results potentially pertaining to a vast array of diseases or traits. Cassa et al. (2012) estimated the number of published disease-associated variants that met the criteria for disclosure to genomics research participants according to published guidelines. Based on their analysis, Cassa et al. (2012) estimated that investigators following these guidelines may be responsible for disclosing over 11,000 variants to each participant.

A specific assay like *BRCA1/2* testing leads to a single result that may inform with high accuracy what one's lifetime risk of developing breast cancer is given mutations in these genes. Such results can be useful to the individual since if they are determined to be at high risk, they may choose to have more routine and thorough exams for early detection or mastectomy or oophorectomy, and it may tune physicians into the increased risk so they are more thoughtful about the interpretation of related exam results. With WGS there may not be any particular condition of interest, but rather a desire to better understand oneself more generally, for example, risk of many different diseases, risk of

nondisease-related traits that may lead to lifestyle changes, ancestry, and other types of personal information that today we can only imagine. Therefore, not only must an individual accept that they could uncover significant risk for any known disease, but also that other unanticipated results may arise, such as learning that your ancestry as determined by sequence data is not consistent with the ancestry your family considers as truth. In the context of understanding one's risk of a particular disease given WGS data, the results likely will not be as clear as a *BRCA1/2* test because the information half-life is very short, i.e., what is known about a specific genetic variant or disease today may be vastly different from that which is known about that variant or disease tomorrow. This makes it difficult to establish and apply guidelines on how to interpret the many hundreds of variants that may be associated with a given disease (Fabsitz et al. 2010; Cassa et al. 2012). How to assess the risk of a disease in the context of hundreds of variants, interactions between those variations and with the environment, and what actions to take given a particular risk score or diagnosis are all similarly complex. All of these factors exemplify that WGS as a diagnostic represents a very different scenario compared to more classic molecular diagnostic assays, with a different set of accompanying challenges for the individual and the researchers/clinicians facilitating that decision.

Patient May not Have Phenotype/Family History of Disease About Which Information Is Produced

In the case of most existing genetic tests such as genetic tests for Huntington's disease, breast cancer, and rare Mendelian disorders, eligibility for testing is determined by the individual having a personal or family history of the disease in question. However, in the case of WGS, particularly with "healthy" individuals, such eligibility criteria are not necessarily applied. This has implications for how prepared the individual may be for the results from WGS. For example, an individual who has a strong family history of breast cancer and who has opted for *BRCA1/2* genetic testing may respond very differently to being told they have a mutation in *BRCA1/2* compared to an individual who learns that they have a very high risk of breast cancer through WGS. While such a discovery may be disturbing, at least there are actions one can take to enable early detection of breast cancer when treatment options and effectiveness are optimal. However, cases will exist in which a significant risk of disease will come to light, but for which little can be done to prevent and/or treat the disease at present. Carriers of the ApoE-e4 allele represent perhaps one of the more obvious cases in which a relatively common allele is strongly predictive of your risk for early-onset Alzheimer's, but for which no preventive treatment can be prescribed at this time.

Of course, positive benefits in a disease context could potentially be realized as well from knowledge of one's sequence data if one is identified as *not* having an increased risk of disease. Knowledge that disease-associated alleles segregating in your family are not represented in your genome may provide for a number of benefits including more informed decisions relating to reproduction, reduced stress and anxiety regarding risk of particular diseases, and more informed diagnoses relating to existing conditions, to name just a few.

Implications for Family Members

Although many genetic tests have implications for family members, this is arguably particularly important in the case of WGS because of the sheer number of results that could be obtained. Learning of one's genetic susceptibility to disease has direct implications for family members who may or may not want to know of such risks. For example, learning that you are an ApoE-e4 homozygote and so at significantly increased risk for early-onset Alzheimer's disease, will have direct implications for your parents and siblings, who may have no desire to learn of such a risk they can do nothing about. These implications go

beyond disease risk for family members, since ancestry (Halder et al. 2008), political beliefs (Hatemi and McDermott 2012), and even being religious or not (Koenig et al. 2005) have genetic components that will increasingly be elucidated as more individuals are sequenced. Thus there is the potential for sequencing data to impact your social network in ways again that most may not anticipate.

Identifiability

Protecting an individual's right to privacy in medicine and research has always been a topic of significant discussion and concern, the primary focus being on the protection of information that is more obviously personally identifiable. DNA information collected on individuals has been of particular concern, given even with anonymized data or de-identified data it will be possible to link such data to a given individual as genetic databases proliferate (McGuire and Gibbs 2006). For example, in 2004, "Lin and colleagues demonstrated that an individual can be uniquely identified with access to just 75 single-nucleotide polymorphisms (SNPs) from that person" (Lin et al. 2006; c.f. McGuire and Gibbs 2006). Thus, decision-making about WGS differs from decision-making about simpler disease-specific tests such as the PSA test because the same promises about protection of privacy and confidentiality cannot, or should not, be made, and the individual needs to take this into account.

As sequencing technologies advance, we will increasingly realize that protecting and ensuring privacy regarding an individual's DNA will not be possible, thus necessitating an even larger focus on educating individuals up front that this will be the case. Equally important will be ensuring individuals are not discriminated against based on DNA information. The protection of personally identifiable information is intertwined with our collective expectation of keeping personal information private. For example, your social security number or data contained within your medical record are both forms of data that are personally identifiable and for which you have a reasonable expectation of privacy. In contrast, although a photograph taken of your face is also clearly personally identifiable, in this case you have no reasonable expectation of privacy in public given we communicate in public by recognizing features such as faces and facial expressions, and given your image is easily acquired via cameras or video recorders.

However, today we are in a state of transition as we figure out collectively how to both understand the information that is personally identifiable and determine what reasonable expectation of privacy we have regarding such data. The social networking revolution has changed our expectations of privacy regarding a great diversity of personal data. Many individuals today disclose highly personal information on the web, loosening our expectations regarding what information should be kept private. Social networking sites like Facebook and Google have ridden this wave and slowly weakened any expectation of privacy we may have regarding information provided to their sites; buried within the consents users click through without ever reading, is their explicit approval to allow these companies to leverage for whatever purpose they deem appropriate any and all personal information, emails, likes and dislikes, political leanings, religious beliefs, and photographs and videos of highly personal scenes in which facial and scene recognition algorithms can be employed to understand your behaviors, your age, your gender, your friends, types of places you frequent, and the types of products you buy. These highly personal data are most commonly used by high-end data analytics firms to better target you with advertising to which you are most likely to respond. The same wants to share all levels of personal details exists in the scientific arena as well, with WGS and deep molecular profiling carried out now on several scientists who have openly disclosed all data with name attached (Ashley et al. 2010; Dewey et al. 2011; Chen et al. 2012).

While continuing to make assurances that we can protect an individual's privacy when DNA are collected as part of a research study, expanding laws, locking down relevant databases, and

creating greater regulatory burdens to further protect privacy represent one set of options. Such steps are likely in vain though as the costs of technologies that can generate high-dimensional data on an individual continue to fall at super Moore's laws rates and as our ability to process big data increases exponentially, as discussed above. In fact, we demonstrated that it is possible to derive genotypic barcodes that can uniquely distinguish among individuals in very large populations, from non-DNA sources (Schadt et al. 2012). Given this growing inability to protect peoples' privacy regarding high-dimensional data that can be easily collected about them, it is imperative to consider alternative strategies. This is especially so if the courts ultimately rule there can be no reasonable expectation of privacy for genomic data, since the ability to acquire your DNA and to sequence it may become as easy and cheap as snapping a photograph of your face. Therefore, we must begin to not only better inform individuals regarding WGS data and their personal privacy, but we must ensure appropriate protections are in place to prevent discrimination based on these data. In the United States, the Genetic Information Nondiscrimination Act and Americans with Disabilities Act provide for many such protections, but as individuals become more empowered to share their data to achieve greater medical benefit from it, and as we move to more seamlessly map between DNA and more easily acquired high-dimensional phenotypic data to predict with greater ease a greater diversity of human behaviors and disease risks, laws must also evolve to ensure the rights of patients are protected (Schadt 2012).

Resource not a Test

Perhaps most important, is the point made eloquently by Biesecker that WGS "is a resource, not a test" (Biesecker 2012). Biesecker highlights that whole genome results are "overwhelming for both the clinician and the patient or research subject," and that we must "disabuse ourselves of the concept that the [WGS] is a unitary diagnostic test" (p. 397). Rather, Biesecker argues, "the burden and challenge of interpreting the potential results should be distributed over the lifetime of the patient/research subject. By changing this approach, one is freed from the apparent obligation to return the results of the entire assay in temporal proximity to its generation … Taken further, a [WGS] dataset can be viewed as a health-care resource that can be interrogated by the patient and clinician in situations where it could be of potential use to the patient, when both agree to this use" (p .397). This paradigm shift has significant implications for decision-making by the individual. Again, rather than making a decision about whether to receive disease-specific test results at a single moment in time, a future patient deciding about WGS may instead be making a decision to have their genomic data generated and then used or stored in many different ways, potentially and to varying degrees controlled by them.

Current Evidence on Decision-Making About Whole Exome/Genome Sequencing

Early studies examined decision-making about clinical and research genetic tests for single diseases such as Huntington's disease (Codori et al. 1994; van der Steenstraten et al. 1994; Creighton et al. 2003), breast cancer, e.g., (Lerman et al. 1996), and Alzheimer's disease (Roberts et al. 2003; Roberts et al. 2004). These studies tended to show that patients' interest in receiving personal results depended on the characteristics of the test and disease (e.g., how predictive of the disease the test is, and how preventable or treatable the disease is), and on individual characteristics (e.g., anticipated ability to cope with adverse results, disease-specific worry) (reviewed in Lerman et al. 2002). Studies such as the Multiplex study at NIH (McBride, Alford et al. 2009; Hensley Alford, McBride et al. 2011; Reid et al. 2012) and the Coriell Personalized Medicine Collaborative (Gollust et al. 2012) have examined decision-making around genetic testing for several SNPs associated with several diseases at a time. Additionally, studies have examined decision-making around DTC genetic tests such as the Navigenics genetic test (Bloss et al. 2010; Bloss

et al. 2011). This body of research to date has tended to suggest that individuals who seek out personal genomic information are primarily motivated by general curiosity, and because they believe it will lead to health improvements (e.g., Gollust et al. 2012). Evidence also suggests that there could be significantly lower uptake of genomic information among non-White populations (e.g., Bloss et al. 2011; Hensley Alford et al. 2011), and that uptake is higher among individuals who are more confident in their ability to understand genetics, and who have more health habits to change (McBride et al. 2009). However, even the studies such as Multiplex (McBride et al. 2009; Hensley Alford et al. 2011; Reid et al. 2012), Coriell (Gollust et al. 2012) and Scripps-Navigenics (Bloss et al. 2010; Bloss et al. 2011) do not begin to get into the myriad of novel challenges arising from WGS, such as the unpredictability of the results, the volume of data produced, and the identifiability of the data with its accompanying implications for privacy or its lack thereof.

Research on decision-making around actual WGS is really only just beginning to emerge. Perhaps the most informative study to date is the ClinSeq project (Biesecker et al. 2009; Facio et al. 2011, 2012; Kaphingst et al. 2012). The initial recruits into the ClinSeq project were individuals with varying levels of cardiovascular disease risk; however, the majority of the close to 1000 participants are healthy subjects. ClinSeq participants sign a broad informed consent, agreeing to have their DNA used for multiple research purposes, up to and including genome sequencing. Facio et al. (2011) examined motivations for participating in the genomics research among a sample of 322 ClinSeq participants: the primary motivations were altruism, and to learn about their own genetic risks of disease (Facio et al. 2011). Facio et al. (2012) then examined interest in receiving personal results from sequencing among a different sample of 311 ClinSeq participants: most wanted to obtain their results, and the main reason given was prevention, including changing lifestyle. Participants had a belief in the value of even uninterpretable information (Facio et al. 2012). Kaphingst et al. (2012) examined the impact of the informed consent procedure on knowledge about genome sequencing in the same 311 ClinSeq participants: they found that knowledge was higher after informed consent than before, and that there were significant differences in knowledge between racial/ethnic and educational attainment groups (Kaphingst et al. 2012). These socioeconomic differences are particularly notable given the majority of participants were white, educated, high-income individuals.

In one small study on patients' attitudes toward actual WGS (Tabor et al. 2012), two families each comprising two parents, and two to three children, were interviewed about their experiences and opinions relating to WGS. Both families were affected with Miller syndrome. Outcomes assessed in the qualitative interviews included opinions on informed consent, motivations and expectations, privacy concerns, and perspectives on return of results. There were few concerns about privacy expressed, although it was noted that these families have different attitudes toward privacy given they already feel like their privacy is limited due to the visible characteristics of the affected family members' Miller syndrome. A range of preferences regarding return of results were expressed. They had strong preferences about how results should be returned, wanting both flexibility of the results return process, and options for the types of results to be returned. Tabor et al. (2012) suggest that "web-based tools that facilitate participant management of their individual research results could accommodate … [a] framework for results return that allows explicitly for participant preferences and enables modifications to preferences over time." Most of the family members interviewed felt that the informed consent procedure was too long and cumbersome (Tabor et al. 2012).

The published empirical research on how patients and research participants make decisions about WGS will undoubtedly explode over the next few years, but is currently limited. In the meantime, it is arguably helpful to turn to non-traditional sources of insights into people's decision-making about WGS and WES. The first individuals to have their entire genomes sequenced and published were James Watson

(Wheeler et al. 2008) and Craig Venter (Levy et al. 2007). Since then, a handful of people in the world have received their personal results from WES/WGS: they have received considerable media and social media attention as a consequence. These include the 10 individuals who had their genomes sequenced as part of the Personal Genome Project pilot (PGP-10) at Harvard led by Church (2005) (Ball et al. 2012), and the individuals who received the raw data and rudimentary interpretation of their WES data from DTC company 23andme (www.23andme.com). Many of these individuals have been writing or talking about their experiences with this in the media or social media such as Twitter (see Fig. 25.1).

These are not, in general, the average person on the street. Many have a professional interest in genetics and genomics. The PGP-10 includes Harvard professor Steven Pinker, genetics professor Misha Angrist, Harvard-educated Esther Dyson, and journalist John Lauerman. The individuals receiving 23andMe exome sequence results include an Associate Professor in biology and bioinformatics (Jung Choi, see https://jchoigt.wordpress.com/2012/07/02/a-first-look-at-my-exome-variants-from-23andme/) and the Vice President of Golden Helix Inc. (Gabe Rudy, see http://blog.goldenhelix.com/grudy/my-23andme-exome-trios-arrived-sneak-peek/).

Fig. 25.1 One individual's post on Twitter about having received his DTC exome sequencing kit (Brett Ryan Bonowicz, BRBonowicz. "Received my @23andme Exome kit today. Very excited." 2 October, 2012, 9.28pm. Tweet)

Many of these individuals have been interviewed about their motivations and experiences of WES/WGS in the media, or have blogged about it in the social media. Examination of these interviews, blogs, and articles can be enlightening.

However, while providing interesting anecdotal evidence, it is not possible to extrapolate from this highly self-selected group of primarily educated, white, male, and often extremely wealthy individuals to the rest of the population. Research examining the motivations, views, and experiences of individuals from a wider range of backgrounds, including Hispanic and African American individuals, and those from lower socioeconomic status groups, is vitally needed. Moreover, the Personal Genome Project was notable for its rigorous entrance examination to ensure that potential participants understood key genetics and sequencing concepts. The PGP has gone to great efforts to develop a new model of informed consent and education for WGS research. However, it excludes individuals who are unable or unwilling to take and pass the entrance exam, which clearly creates a problem of unequal access across society to the benefits potentially afforded from WGS moving forward. Given the paradigm shift in the genome sequencing age, new models and methods of educating and obtaining informed consent from individuals considering participating in WGS research, or obtaining WGS results for personal clinical or other use, are needed. These methods must be accessible and relevant to individuals from a range of educational and cultural backgrounds.

Interventions to Aid Decision-Making About Genome Sequencing

The traditional approach to helping patients make informed decisions about receiving personal genetic results involves intensive, one-on-one genetic counseling. However, this is

unsustainable as genome sequencing becomes commonplace. Patient decision aids may be one helpful approach to increase informed decision-making about personal WGS. Patient decision aids prepare people to participate in "close call" decisions that involve weighing benefits, harms, and scientific uncertainty (O'Connor et al. 2009). Patient decision aids are widely used to help patients make complex decisions related to their health and health care, and can come in a variety of formats, including pamphlets, brochures, videos and interactive computer-based formats.

In a recent systematic review of decision aids for people facing health treatment or screening decisions, patient decision aids were shown to perform better than usual care interventions in terms of leading to greater knowledge, lower decisional conflict relating to both feeling uninformed and feeling unclear about personal values (O'Connor et al. 2009). For example, in a large randomized controlled trial an interactive computer program was more effective than standard genetic counseling for increasing knowledge of breast cancer and genetic testing among women at low risk of carrying a *BRCA1* or *BRCA2* mutation (Green et al. 2004).

Additionally, another recent systematic review focusing specifically on computerized patient decision aids showed that computerized patient decision aids performed better than standard consultations/education regarding improved knowledge, lower decisional conflict, and greater satisfaction with the decision-making process than standard education (Sheehan and Sherman 2012). Computerized decision aids have the advantage of readily tailoring information to individual user characteristics, enabling feedback to reinforce comprehension, incorporating interactive and advanced visual features to facilitate participant involvement, and disseminating information easily (Sheehan and Sherman 2012).

The International Patient Decision Aids (IPDAS) Collaboration was established at the 2nd International Shared Decision Making conference in 2003. The IPDAS objective was to develop a set of quality criteria for patient decision aids. The retained criteria were in the following domains: systematic development process; providing information about options; presenting probabilities; clarifying and expressing values; using patient stories; guiding/coaching; disclosing conflicts of interest; providing Internet access; balanced presentation of options; using plain language; basing information on up-to-date evidence; and establishing effectiveness (Elwyn et al. 2006).

The IPDAS Collaboration strongly endorsed the *values clarification technique* of describing the physical, emotional, and social effects of options to help patients to explore "experienced utility" (Elwyn et al. 2006). Values clarification exercises have been developed as part of a decision aid for the treatment of early-stage prostate cancer (Feldman-Stewart et al. 2006), and as part of a computerized decision aid for low literate and naive computer users, newly diagnosed with early-stage breast cancer, recruited from two urban public hospitals (Jibaja-Weiss et al. 2006).

Jibaja-Weiss and Volk (2007) posit that even interactive computerized decision aids are often heavily reliant on written information, health and digital literacy, and advocate for using entertainment education (or "edutainment") as a means of promoting informed decision-making among patients with low health literacy (Jibaja-Weiss and Volk 2007). Edutainment is the process of purposely designing and implementing media that incorporate educational messages within an entertaining format, and to date has largely focused on using a "'soap opera" format. Computerized entertainment education has been used to aid decision-making about prostate cancer screening among men with low health literacy (Volk et al. 2008), and to aid decision-making about breast cancer surgery among women with low healthy literacy (Jibaja-Weiss et al. 2011).

At the Icahn School of Medicine at Mount Sinai (ISMMS) in New York City, we and colleagues developed a novel animated video about WGS that was developed specifically to be accessible to individuals from a range of socioeconomic and racial/ethnic backgrounds, using elements of the entertainment education

process (Sanderson et al. 2016). The video was designed to be used as a general public education resource and is publicly available on YouTube. It was also designed to be useful as a communication and educational tool for genetic counselors interacting with patients or research participants considering having personal WGS done (see Fig. 25.2). The video was developed in an iterative manner. To develop the initial draft script, we drew on publicly available sources about genetics and genome sequencing, including the "Help Me Understand Genetics" handbook by the U.S. National Library of Medicine (http://ghr.nlm.nih.gov/handbook.pdf), the education section of the NHGRI website (http://www.genome.gov), and the Personal Genetics Education Project website at Harvard (www.pged.org), and also involved experts from a range of relevant backgrounds, including genetic counselors and other genetics experts. An early draft of the script was piloted with 10 racially/ethnically diverse patients at an outpatient clinic at MSSM. In addition, an online text and example graphics version was piloted with 173 racially/ethnically diverse individuals recruited through an online market research company. The draft animation was then developed with a Manhattan-based animation and design company, and then shown to four Hispanic and African-American community consultants. Revisions were made in light of the feedback we received, and the next draft of the animation was shown to 22 individuals in three focus groups. The individuals were recruited from communities surrounding ISMMS, and were primarily Hispanic and African-American. Revisions were subsequently made in light of this next feedback (Sanderson et al. 2016), and the final animation is freely available on YouTube (see https://www.youtube.com/watch?v=IXamRS85hXU&hd=1). We subsequently used the animation with participants recruited into the HealthSeq project at ISMMS in which they were offered personal results from WGS (Sanderson et al. 2016). The animation we developed is an example of a new generation of efforts to use new media to educate the public, and to aid healthcare providers as they strive to help patients and research participants understand personal genomics. Another example of an animation designed to explain about developments in genomics is the short animation explaining what the ENCODE project is in lay terms, funded by Illumina and created by Cartoonbrew (www.cartoonbrew.com/tag/dc-turner). This animation is also available on YouTube.

In summary, genetic counseling services to aid decision-making about genetic testing and genome sequencing are already stretched. Patients are likely to ask their primary healthcare providers for help interpreting their genomic test results, even if obtained outside the clinic setting.

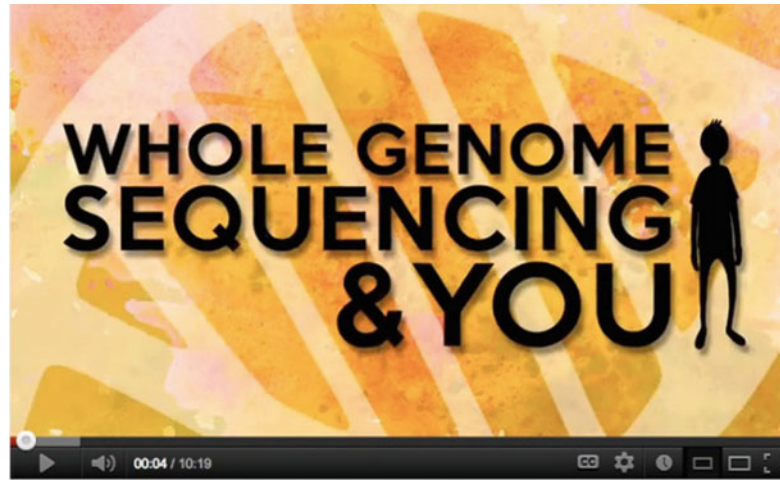

Fig. 25.2 A still from a 10-min animation explaining what whole genome sequencing is

New and innovative models to educate patients and facilitate informed decision-making are needed. Patient decision aids such as animations and interactive media may go some way to improving informed decision-making without leading to undue burden on the healthcare system (e.g., by insisting on hours of one-on-one genetic counseling per patient). However, important questions remain about how best to achieve this, and evidence-based innovative interventions are urgently needed to create a genomics-literate public capable of making informed decisions about WGS without putting unnecessary burden on them or their healthcare providers.

Privacy and Open Informed Consent

Informed consent forms one of the cornerstones of research involving human. The standard practice for enrolling participants in a research study include fully informing potential participants on all aspects of a study including the aims of the study, risks, benefits, costs, and protection of personal privacy. The origins of modern day informed consent for medical research can be traced to the Nuremberg Code in 1947 in an effort to protect participants in research studies. However, the omics revolution combined with a far more open data sharing mentality permeating many aspects of society today (see section on identifiability above) are driving a new generation of informed consents that put the study participant's ability to openly share data generated on them front and center. Classic consents that ensure or even guarantee the privacy of the individual are being challenged by these new consents that aim to educate participants on what the data collected on them can say and the degree to which it can or cannot be protected, while simultaneously empowering the individual to take a more vested interest in research outcomes as well as giving them more control over sharing of their own data with others and with scientists in particular (Box 1).

This "open informed consent" movement is evolving to accommodate the view that many patients want to share their data generated for research with others, to further enable the scientific community to solve problems relating to their condition without being unnecessarily hampered by restrictive rules that prevent, in the name of privacy, a patient from benefiting more directly from data they contribute. The portable legalized consent (PLC—http://weconsent.us/) now approved for use by Sage Bionetworks is just such a step in this direction. The PLC seeks to appropriately educate research subjects and then enable them to have more control over the use of data generated on them for research or other purposes. The PLC not only provides for more informed study participants that better understand the risks and rewards involved in making their data available to others, but it has the potential to facilitate a more productive research environment as research subjects become entitled to not only receive the data generated on them (it is nearly inexplicable that research subjects have not had this right before) but to share it with any others who are willing to follow commonsense rules regarding use of the data. Educating research participants appropriately on what data collected on them can say and the degree to which it can or cannot be protected, and then empowering research participants to have a more vested interest in outcomes and the ability to empower other scientists with *their* data, is definitely a step in the right direction.

Challenges and Recommendations

The age of genome sequencing is bringing with it a complete paradigm change in how we think about patients' and research participants' decision-making about whether to obtain personal WGS, whether to participate in WGS research, and receiving personal results from WGS. No longer can we provide individuals with information about one disease and one test, measure their feelings about that disease and the test being offered, assess at one time point whether or not they take up the offer of that test for that disease, and assess the outcomes of that decision in a simple linear fashion. Informed consent documents and procedures for WGS will

need to emphasize that privacy cannot be guaranteed, and that the purposes for which the sequence data will be used cannot be predetermined. Both of these messages are in direct opposition to current approaches to informed consent. Traditional genetic counseling models involving hours of in-person counseling will need to be replaced or enhanced with innovative media-based interventions that are accessible to individuals across society. The results from WGS will not be returned to individuals at one single moment in time; rather, interpretation of WGS data for any given individual will be a continuous, dynamic process over time. This poses significant challenges for researchers and clinicians alike, for whom new models of research and clinical practice will be needed to adapt to this changing landscape and timeline of interaction with patients and research participants. As Holly Tabor and colleagues suggest, the return of results to patients/research participants will likely need to utilize dynamic web-based platforms that can incorporate and be responsive to patients/research participants' preferences regarding the types of information they would like to receive over time (Tabor et al. 2012). In addition, a new generation of researchers and healthcare providers will be needed who are genomics savvy and able to deal with the deluge of genomic information that is coming. This includes social and behavioral science researchers who will need a deep understanding of WGS in order to be able to work with others to develop the information and educational materials, to develop the methods for returning the results to patients/research participants, and to assess decision-making among individuals who are offered personal WGS, as well as the cognitive, emotional, and behavioral outcomes of those decisions. In addition, WGS is leading us to an age where genomics will no longer be just about disease and illness, but will touch every aspect of people's lives, providing information on their ancestry, their health behaviors, their mood, and their psychological functioning. Appropriately dynamic, evolving and preference-sensitive informed consent models, educational interventions, and return of results delivery formats are going to be needed if the promise of genomics is truly to be delivered.

Box 1. Current Generation, Open and Interoperable Informed Consents (from Schadt 2012)

Current Generation Informed Consents

- Often single study focused
- Top-down unidirectional researcher–participant (research subject) relationship
- Protecting the participant considered among the chief aims
- Data generation on study participants usually an integral part of the consent
- Data ownership and terms of use driven by the investigator and/or hosting institution
- Study participants are counseled to ensure they understand all aspects of the study, although no evidence of understanding is sought or required
- In most cases, anonymity, privacy, and confidentiality are guaranteed as key conditions for a participant's consent.

"**Open Consents**" **for public resources**: **The Personal Genome Project Consent (Church 2005; Lunshof et al. 2008)**

Open consent differs from classic informed consent in the following ways:

- Data ownership and terms of use of data no longer driven by study investigator
- Data are published to the web and made available without restriction
- Single study focused, but has broad and open-ended scope (data sharing as an aim)
- Participants agree to reciprocal interaction with researchers
- Participants must pass an exam to ensure they possess basic genetic literacy, are informed about the public nature of the study, understand the possibility of reidentification, and that some risks are unknown and unpredictable.

Interoperable and Open Consents: The Portable Legal Consent (PLC) (http://weconsent.us/) Based upon the PGP consent, but altered in the following important ways:

- The PLC can be used across any number of studies
- If variations of the same PLC form guarantee the same freedoms and create no more than the same obligations, it can be certified as interoperable across the PLC network
- Fully digital, requires no input from a physician or other health/research professional
- Requires users sign terms of a contract to ensure compliance with data use terms
- Intended for data already generated, to enable open access of data across many studies.

Summary Box

- Whole genome sequencing (WGS) could be routinely available to patients for a few dollars within the next 10 years.
- The volume of data produced by WGS is unprecedented, and the types of results that an individual may receive through WGS are unpredictable and open-ended.
- This has important implications for decision-making about WGS: decisions have to take account of the unpredictability of the results, the volume of data produced, and the identifiability of the data with its accompanying implications for privacy or its lack thereof.
- The traditional, intensive, one-on-one genetic counseling approach to helping patients make informed decisions about receiving personal genetic results is likely to be unsustainable as WGS becomes commonplace.
- New and innovative models to educate patients and facilitate informed decision-making are needed: animations and interactive media may be valuable resources fulfilling this need.
- A new generation of genomics-savvy social and behavioral science researchers is needed to develop the educational materials and methods for returning results to patients and research participants; to assess decision-making among individuals who are offered personal WGS; and to assess the cognitive, emotional, and behavioral outcomes of those decisions.

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