

# Tip-toeing into the world of genomics: Ethics of gene sequencing in clinical medicine

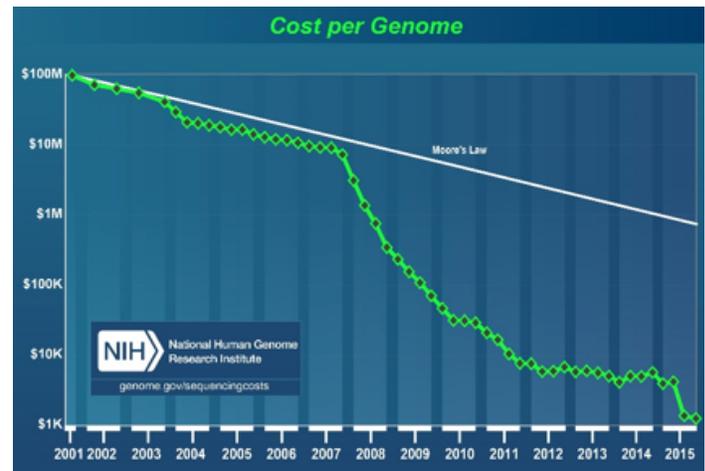
Jasper Johar<sup>1</sup>

Citation: UBCMJ. 2017; 9.1 (31-33)

Hippocrates is often credited with being the first to separate patients into groups and individualizing treatments based on each group's predicted response.<sup>1</sup> This ideology is known as “personalized medicine,” and has in recent times seen a renaissance due to modern advancements in biotechnology. In 1990, the National Human Genome Research Institute (NHGRI) announced the commencement of the Human Genome Project to sequence and map out 100% of the genetic information of a human being, which is commonly referred to as the human genome.<sup>2</sup> The project was completed on April 14th, 2003, almost 13 years later. At the present date, we can now sequence a human genome in as little as 26 hours.<sup>3</sup> The cost of sequencing a genome has also dropped significantly from \$100M in 1990 to approximately \$1000 USD in 2015 (Figure 1). Genomic sequencing has become so fast and affordable that sequencing a patient's genome to make clinical decisions is well within reach. Many gene loci are implicated in disease, and some varieties of gene loci respond to treatments with differing efficacy. By tailoring therapies to a patient's genetic code, we have the potential to create better management guidelines that inform more appropriate clinical decisions at the point of care. However, with access to abundant amounts of genetic information one must be careful with what information they uncover. Accidentally finding markers for diseases that have no effective means of prevention or treatment can do harm to patients without improving their health outcomes. Also, if patients are to have their genomes sequenced to better their health outcomes in the future, one must wonder who holds ownership of this genetic information and how this information will be stored and used. Lastly, making genomic sequencing a medical norm could have unforeseen consequences both socially and economically that may impact all of us and how we live our lives. Considering the above, much thoughtful planning is warranted when implementing genome screening programs.

Personalized medicine informed by genomics already exists today in modern clinical practice. For example, a patient with a particular family history can raise flags to prompt genetic testing. An example of this could be a female patient with several family members who have had breast and ovarian cancers that were diagnosed early on in their lifetimes. A referral to medical genetics could unveil that the patient is a carrier for mutations in the *BRCA1* and *BRCA2* genes. Carriers of mutations in these tumor-suppressing genes are known to be at a significantly increased risk for breast and ovarian cancers.<sup>4</sup> Screening these patients and intervening is particularly useful, as there is evidence that early screening and interventions such as bilateral prophylactic oophorectomy and mastectomy in *BRCA1* and *BRCA2* mutation-positive individuals decreases their incidence of cancer.<sup>5</sup>

When genomics yields results by screening for a few gene loci, it can be all too tempting to screen the entire genome to see what



**Figure 1** | Cost of sequencing a genome from 2001-2015. Moore's law here approximates the cost savings involved with the doubling of computing power every year which is the standard in the computer hardware industry. The rapidity of decline in costs of genomic sequencing relative to Moore's law highlights its massive success.<sup>18</sup>

other mysteries lie in our DNA and how we can take control of our destinies to improve health outcomes. This temptation is reaffirmed by the commitment of \$25 million USD over five years towards four projects on genomic screening in infants by the National Institute of Child Health and Development and the NHGRI.<sup>6</sup> One of the projects, named the BabySeq project, is currently underway at Brigham and Women's Hospital and at Boston Children's Hospital. Half of the 240 recruited newborns will be placed into control groups that will receive the current standard heel prick blood test that screens for approximately 30 heritable and treatable diseases, while the other half will receive full genome sequencing.<sup>6</sup> This project may find exciting new genes that correlate with disease and response to medical treatments, which can provide deeper insights into clinical judgements and improve patient outcomes. However, what happens with pathological genomic data that may be uncovered by genomic sequencing that we cannot change the outcome of? For example, the genomic sequencing of an infant could show that they carry the autosomal dominant huntingtin (HTT) gene for Huntington's disease (HD), a rare but devastating neurodegenerative disease that has an average life expectancy of 10 to 15 years from its onset of symptoms.<sup>7</sup> This is not particularly useful information since there are no known means of preventing HD, and thus this can cause unnecessary anxiety and suffering for the patient. Some parents who suspect that their child may have the HTT gene have looked into screening their child for it to inform their future financial decisions, such as not putting money aside for a college fund if their child is expected to develop HD.<sup>8</sup> The current guidelines from the Huntington's Disease Society of America have strongly opposed screening children for the above psychological and social harms and lack of benefits.<sup>9</sup>

It is difficult to reconcile established guidelines of the past with new advances in genomics. In the guidelines provided by the American

<sup>1</sup>MD Program, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada

Correspondence  
Jasper Johar (jasper.johar@alumni.ubc.ca)

College of Medical Genetics and Genomics (ACMG) it is mentioned that child screening for adult-onset diseases is consistently cautioned against in the literature. However, the ACMG also argues that these policies are difficult to reconcile with the realities of genome sequencing in this transitional period of adopting genomic medicine. They argue that these practices are inconsistent with respecting a parent's right to make decisions about their children's health, and genomic results may have implications on the lives of the parents and family. Healthcare providers have an obligation to inform parents and the child, when appropriate, about these potential implications. This statement suggests an important consideration in the era of genomic medicine; after sequencing a child for a primary indication, it becomes relatively easy for a laboratory to report a limited number of variants for conditions that could be medically important to that child's future or to the rest of the family. The ACMG also mentions that one possible solution would be to restrict the sequencing and omit genes associated with diseases for which there is no available treatment.<sup>10</sup> On the contrary, it could be distressful for a patient who had their entire genome sequenced only to find out that they had a gene variant omitted in their screen that resulted in them presenting with a debilitating disease later in life. Therefore, guidelines must be set out and clearly expressed to both the healthcare team and the patient stipulating why this information would be omitted and possibly leave the option open for the patient to sequence genes for such diseases when they come of age and if they choose to.

Another nuanced issue regarding genomic sequencing is the opportunity to uncover genomic data that has uncertain clinical implications. For example, if a genomic screen were to uncover that a patient carried the recently discovered *CLU* and *PICALM* genes and were at a slightly increased risk for developing Alzheimer's disease, what would the physician do?<sup>11</sup> Some may argue that certain patients would want to know this information as they may choose to live their lives differently given a different life expectancy or quality of life. However, there are no known means of primary prevention for Alzheimer's disease and the patient may never present with the disease as its association with Alzheimer's is only a correlation. Thus, complete genome sequencing may be over-diagnosing patients, again leading to unnecessary worry for the patient and potentially causing unnecessary follow-up testing and inappropriate use of healthcare resources. Once more, patients should retain the right to know this information should they choose to. However, it is important to note that patient education has a critical role to play in genomic screening, so that patients are able to fully understand and appreciate the consequences of learning this information about themselves and its usefulness in their goals of care. In addition to the issues of what one may uncover by collecting these data, another big question is who owns these data? The most natural answer would be that the individual who provides the tissue sample owns the data related to it. However, with current precedent there are many barriers for patients to access their medical information due to the lack of user-friendly Electronic Medical Records.<sup>12</sup> Therefore, once a person's genome is sequenced, anonymized, and stored by a Large-Scale Genome Sequencing and Analysis Centre it is conceivable that patients will not be able to access their genomic data and must rely on Direct-to-Consumer genome sequencing services such as Navigenics and 23andMe for their genomic information.<sup>13</sup>

Lastly, as genome sequencing becomes the norm in medicine, its technology and knowledge will spread broadly. DNA sequencing

technology is currently widely available commercially, and anybody can use it.<sup>14</sup> The prospect of open access to genomic screening could potentially raise concerns with how it is used. Its usage is difficult to regulate and thus there may be parts of the world that decide to use genomic sequencing to discriminate individuals based on their genomic background. Insurance companies could charge high premiums or even refuse to insure individuals who are at high risk for certain conditions.<sup>8</sup> Before a patient submits their genetic samples to be sequenced, it is critical that companies make it clear to patients what rights to their own genome that they are revoking and how their genomic data will be used and who it will be shared with. Legislation already exists to protect people from such genetic discrimination in developed countries like the United States, but this may not be the case in other countries. In Guangdong, China, three civil servant candidates claimed to be discriminated against during a recruitment process for carrying a gene associated with thalassemia, which is a common gene carried in approximately 11% of the Guangdong province.<sup>15</sup> The court ruled that thalassemia is a disease and thus it is legal for employers to use it as one of their requirements for recruitment, despite the plaintiff being only carriers for the gene of the disease. This example is one of many around the world illustrating that although legislation protecting against genomic discrimination likely exists, its enforcement may vary from region to region.<sup>16,17</sup>

The medical profession looks to alleviate suffering and do right by their patients. Impassioned by the drive to create better medicine for patients, medical research has created technological innovations to uncover many different medical conditions, and causes for them. However, by doing so we may be unknowingly creating ethical quagmires. Before making genomic sequencing commonplace in medicine, some thought should be given to how it could affect our lives socially, economically, legally, as well as medically. Moving forward, it may be prudent to design genome screening programs that "black-box" genes that may cause more harm than good should that gene be known to the patient. This black-box status could be removed if the patient expresses that they wish to know the status of such genes; however, this process should be accompanied with the guidance of a health professional who can explain the benefits and risks of knowing such information. In this way, patient autonomy can still be respected while mitigating potential risks. Also, as a part of their medical record, a patient's genetic information should be readily available to them in a user-friendly format. Apps and mobile platforms that are secure and allow the patient to view their genome can potentially fill this void in the future. In concordance with current precedent surrounding the genomic screening of minors, patients making decisions regarding their genomic information should also be of a legal decision-making age. Such a genome screening program should also be evaluated often, so that it may keep up with the rapid pace of technological growth while still providing quality care. Biotechnology has vastly improved over the past few decades by leaps and bounds, and is expected to continue growing in the future. However, when it comes to implementing breakthrough technologies such as genomic screening in the clinical setting, we may be better off tip-toeing our way into the world of genomics.

## References

1. Offit K. Personalized medicine: new genomics, old lessons. *Hum Genet.* 2011 Jul 1;130(1):3–14.
2. About NHGRI: A Brief History and Timeline [Internet]. National Human Genome Research Institute (NHGRI). [cited 2017 Mar 4]. Available from: <https://www.genome.gov/10001763/About-NHGRI-A-Brief-History-and-Timeline>

3. Miller NA, Farrow EG, Gibson M, Willig LK, Twist G, Yoo B, et al. A 26-hour system of highly sensitive whole genome sequencing for emergency management of genetic diseases. *Genome Medicine*. 2015;7:100.
4. BRCA1 & BRCA2: Cancer Risk & Genetic Testing [Internet]. National Cancer Institute. [cited 2017 Mar 18]. Available from: <https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet>
5. Breast Cancer after Prophylactic Bilateral Mastectomy in Women with a BRCA1 or BRCA2 Mutation — NEJM [Internet]. [cited 2017 Mar 4]. Available from: <http://www.nejm.org/doi/full/10.1056/nejm200107193450301#t=article>
6. Kaiser, J. NIH Studies Explore Promise of Sequencing Babies' Genomes [Internet]. Science. 2013 [cited 2017 Mar 5]. Available from: <http://www.sciencemag.org/news/2013/09/nih-studies-explore-promise-sequencing-babies-genomes>
7. Reference GH. Huntington disease [Internet]. Genetics Home Reference. [cited 2017 Mar 18]. Available from: <https://ghr.nlm.nih.gov/condition/huntington-disease>
8. Dean M. Human Genetic Screening [Internet]. [cited 2017 Mar 5]. Available from: <https://www.ndsu.edu/pubweb/~mcclean/plsc431/students99/dean.htm>
9. Nance M, Myers R, Wexler A & Andrea Zanko. Genetic Testing for Huntington's Disease Revised HDSA Guidelines. *Athena Diagnostics*; February 2003 p.18.
10. Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med*. 2013 Jul;15(7):565–74.
11. Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat Genet*. 2009 Oct;41(10):1088–93.
12. Cimino JJ, Patel VL, Kushniruk AW. What do patients do with access to their medical records? *Stud Health Technol Inform*. 2001;84(Pt 2):1440–4.
13. Foster MW, Sharp RR. The contractual genome: how direct-to-consumer genomic services may help patients take ownership of their DNA. *Personalized Medicine*. 2008 Jul;5(4):399–404.
14. Kaye J. The regulation of direct-to-consumer genetic tests. *Hum Mol Genet*. 2008 Oct 15;17(R2):R180–3.
15. McEwen JE, Boyer JT, Sun KY. Evolving approaches to the ethical management of genomic data. *Trends Genet*. 2013 Jun;29(6):375–82.
16. DNA Sequencers | New and Used DNA Sequencers, Protein Sequencers | LabX [Internet]. [cited 2017 Mar 4]. Available from: <http://www.labx.com/dna-sequencers>
17. Genetic Discrimination [Internet]. National Human Genome Research Institute (NHGRI). [cited 2017 Mar 4]. Available from: <https://www.genome.gov/10002077/Genetic-Discrimination>
18. NHGRI. The Cost of Sequencing a Human Genome [Internet]. National Human Genome Research Institute (NHGRI). [cited 2017 Mar 18]. Available from: <https://www.genome.gov/27565109/The-Cost-of-Sequencing-a-Human-Genome>