GENOMICS SEQUENCING AND PRECISION MEDICINE – ARE WE READY?

ETHICS CONSIDERATION, CURRENT GUIDANCE AND FUTURE TRENDS

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BENEFIT OF GENOMICS SEQUENCING TO PRECISION MEDICINE

Genomic sequencing has been grabbing headlines recently with promises of potentially improving medical practice by tailoring the preventive, diagnostic and therapeutic care available to each patient. Genomics is the cornerstone of the cutting-edge precision medicine programs aimed at eradicating cancer and other high-impact diseases and has a significant impact on improving more generalized patient outcomes.

Medical breakthroughs are likely to involve genetic-based immunotherapy, genome-editing technology (CRISPR) or cancer vaccines, just to name a few. For example, the potential universal cancer vaccine involves injecting tiny particles of genetic code into the body that travel to the immune cells and teach them to recognize specific cancers.\(^2\)

This is another step on the road to personalized medicine—treatments tailored to individuals based on the specifics of their body, genetics and the disease in question. With this information, a doctor might know exactly which unique combination of drugs and chemotherapy would best target a patient’s cancer, which could be different from another person with the same symptoms. With more than 200 types of known cancer, linked to a wide variety of causes, such precision is needed.\(^3\)

The Precision Medicine Initiative (PMI)\(^4\) is banking on the industry’s growing comfort with Big Data analytics as the foundation for a concerted effort to gather patient data into a centralized repository that can be used and reused for research purposes, potentially generating insights into Alzheimer’s disease, autism, diabetes, heart disease and other impactful conditions.

GENOMICS SEQUENCING FOR RARE DISEASE SUFFERERS ONLY OR THE ENTIRE HEALTHY POPULATION?

Most large-scale research projects target people with diagnosed conditions or rare diseases (e.g., the 100,000 Genomes Project,\(^5\) and G2P\(^6\)), the projects targeting healthy people with general access have only just becoming accessible but are under heavy scrutiny (e.g., 23andme\(^7\)) from the Food and Drug Administration (FDA).\(^8\) Whole genome sequencing is being used primarily for cancer treatments and to find the molecular etiology of mysterious illnesses that are suspected of being genetic. What hasn’t been done is integrating personal genome sequencing into our everyday lives and routine medical care.

Unlike gene tests intended to identify the cause of a suspected or diagnosed genetic disease, a growing number of projects known as predispositional personal genome sequencing, or PPGS,\(^9\) aim to identify risks such as heart disease and cancer and provide other potentially useful personal information to ostensibly healthy people.

The rapidly dropping cost made general sequencing accessible for the healthy population. Although it is possible that genomic sequencing is used for risk predictions to make positive behavioral and lifestyle changes, there is a danger that the results could be distressing without any benefit, and false positives or uncertain results could prompt unnecessary and expensive follow-up care. What is still controversial is to what extent sequencing or other genomic technology can help with predicting disease because few clear-cut examples have any evidence that having genomic information makes any difference in a person’s life.
So what are the wider ethical and legal implications of genomic sequencing for individuals and society? How is genomic information disclosed, shared and used?

**ETHICAL CONSIDERATIONS**

Genomic sequencing is largely used as a screening tool. What if people misinterpret or overreact to their results and spend their money or take health risks trying to address a condition they might never actually develop? And what if those types of insurance that are not currently protected by law start discriminating against individuals who learn of new and previously unanticipated genetic risk factors? If a report shows any genetic mutation or increasing risk of any condition, would a person want to know whether a cure is available? Will a precision medicine be developed in time to save that person? Or what can that person do to persuade scientists and public funding to prioritize his or her “risk”? Can anything be done to change this destiny?

What if low-risk results cause some people to become overjoyed about their health and start heavy smoking, drink more, have a poor diet and stop exercising because they were born with a “good hand of cards”? Social problems from these behaviors are more profound than individual health. Revealing genomic information certainly has a wider societal impact beyond the individual receiving it.

Perhaps the most important unanswered question is whether the presumed utility of PPGS will prove true. Will learning genetic risk information save lives, or could it produce more harm than good? If a result shows genotype markers that “raise” your risk of cancer from 24% to 30%, does a person undergo additional MRIs, X-rays and biopsies, hence exposing him or her to more radiation, which cause more cancer and burden of illness, or opt in for more invasive treatment, such as a mastectomy like Angelia Jolie?

We have very little evidence to answer these questions, yet healthy diet or exercise is suggested to just do as much good as aggressive intervention therapy.

How do we start tracking the outcomes of those individuals who are arranging to be sequenced out of curiosity or in the hopes of preventing future illnesses? We as a society are not prepared.
REGULATORY GUIDELINES AND GENOMIC PRIVACY
Regulations are usually one step behind scientific innovations. The FDA generally embraces the concept of genomic sequencing and precision medicine. The FDA’s role is to ensure the accuracy of genetic tests, many of which are derived from next-generation sequencing (NGS), a rapid and fairly inexpensive technology that collects data on a person’s entire genome. Researchers are combing through segments of these data to look for genetic variants, potentially meaningful differences that might eventually result in a treatment. However, the vast amount of information generated through NGS poses novel regulatory issues for the FDA. Before detailed guidelines are published, a platform precisionFDA and the Genomics and Targeted Therapy Group are created, working to advance the application of genomics in the discovery, development, regulation and use of medication. The FDA ordered 23andme to stop selling its personal genome service (PGS) in 2013 and only permits marketing of first direct-to-consumer genetic carrier test for Bloom syndrome carrier status in 2015, suggesting the FDA is closely monitoring this topic yet reluctant to give total market control.

In Europe, European Medicines Agency (EMA) issued draft International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline E18 on genomic sampling and management of genomic data in 2016 to provide harmonized principles of genomic sampling and management of genomic data in clinical studies. This guideline also aims to facilitate the implementation of genomic studies by enabling a common understanding of critical parameters for the unbiased collection, storage and optimal use of genomic samples and data. Further objectives of this guideline are to increase awareness and provide considerations regarding subject privacy, data protection, informed consent and transparency of findings.

As genomes cover both human tissue samples and data information regulations, it is detailed in both human tissue acts and privacy legislations.

Genomic Data Privacy

In terms of privacy, genomic data are not explicitly listed as a HIPAA identifier in the United States, but “biometric identifiers” is. At the moment, if a non-scientific random individual got hold of some genomic sequencing data, it is unlikely these data could be used as biometric identifiers. However, with the unprecedented speed of sequence database development, this can happen in the very near future. After all, fingerprints are within the biometric identifiers category, and saliva samples won’t be harder to obtain.

In the EU, where privacy legislation is strict and broader, “biomedical state of the data” will be an umbrella covering genomic data under the personal health data category and making it subject to the General Data Protection Regulation (GDPR). Emphasis is placed on informed consent for genomic data, and it may be destroyed upon participant request. Genomic data should be treated with the same high standards of confidentiality as other clinical data, which are single-coded and do not carry any personal identifiers. Anonymization, as defined in EMA ICH E15, is not recommended for genomic samples or data because the process renders the ability to connect previously unlinked genomic data to phenotypic data impossible. In addition, anonymization does not allow for sample destruction pursuant to withdrawal of consent or for long term clinical monitoring.
GUIDELINE IN PRACTICE

In reality, different countries, practices and ethics committees have their own interpretation of these limited early-stage guidelines. For example, if a doctor is uncertain the diagnosis or cause of a patient’s sickness (e.g., chronic headache), a genomic report can be ordered. How do they deal with accidental findings (e.g., a mutated gene TP53 which can cause Li-Fraumeni syndrome, a rare, inherited disorder that leads to a higher risk of developing certain cancers)? The ethics guideline in the UK advise a doctor must tell the patient for the benefit of the patient’s interest as it is perceived as unethical not to (patients can be prepared and have a chance to have their affairs in order). In France, on the other hand, the doctor is not only must keep his or her silence but is not even supposed to look beyond what is in the scope of care (headache in this case) for the same reason – the patient’s interest, because a healthcare provider’s (HCP) duty is to treat a patient as the complaint but not inspect anything outside of that. In China, such findings are communicated to the family, not even the patient himself, again for the same reason of protecting the patient’s interest, as he might not take the bad news well and his family can give his the best care.

Perhaps the most human method is to respect patients’ desire and consent, how they would like to be communicated with on accidental findings and whether care afterward will be provided or available. But such tasks will involve intense administration, thorough understanding of the genomic findings or fully trained HCPs, who may not equipped to do so.

Doctors in general don’t recommend genomics sequencing as their standard practice unless they have evidence to suspect the disease is genetic related. Some of the main concerns are doubt of the accuracy, worry about misinforming people about the risk of disease and not being trained to give advice.

Concerns about the potential harm in sequencing the genomes of healthy people come as new companies vie to provide such services for the general public. An average person could carry about 54 genetic mutations that are considered lethal but that don’t seem to harm their health. As a result, physicians don’t know what to tell healthy people who harbor these variants.

SHARING GENOMIC INFORMATION IS NO LONGER A PERSONAL DECISION

In a study conducted by Harvard Personal Genome Project, over 98% of participants take part in the program because of curiosity and personal interest, and 71% of providers are very happy to share. However, some staffers who declined to participate after initially agreeing are being surveyed for their reasons and concerns, such as privacy and the possibility they might receive unwanted information. When an individual shares his genomic data, or publishes his genomic report on public domain, he is disclosing extremely sensitive personal information of his parents, siblings and (future) children as well. Have all of these parties given informed consent on sharing and publishing their genomic data forever? Curiosity and personal interests might put our family and loved ones in unknown territory.
THE INTEGRATION OF GENOMIC SEQUENCING INTO HEALTHCARE DOESN’T FIT VERY WELL IN THE MODEL OF HOW MEDICINE IS PRACTICED TODAY (TREATMENT FOCUSED)

GENOMIC SEQUENCING USED FOR TREATMENT OR PREVENTION

The integration of genomic sequencing into healthcare doesn’t fit very well in the model of how medicine is practiced today (treatment focused) but is well aligned with the future vision of healthcare that so many of us have — a vision that focuses upon prediction and prevention.

Personal genome sequencing will play a central role in bringing a more personalized and participatory form of medicine — including a healthcare system in which patients have more knowledge of their own risks and diagnoses and are empowered to act upon that information. If so, it makes more sense sequencing the entire population for all sorts of conditions, even diseases for which they have no known family history, not just people who are sick or have rare genetic diseases. Earlier discussion shows this might not be a good idea with no consequences whatsoever.

However, from the point of humanity’s health alone, sequencing the entire population is very tempting (PPGS as discussed earlier). The broad aim is to understand people’s genetically based risks and develop strategies to keep them healthy, rather than just treating their diseases, as well as to identify genetic variants that might affect the way an individual responds to medications, a science known as pharmacogenomics. It is not a common practice yet despite its potential benefit. While many groups of sick individuals, and some cohorts of healthy people, have been sequenced, only a small number of people (approximately fewer than 2,000) have been sequenced and received their results afterward. To date, no large-scale study has systematically tracked seemingly healthy individuals for the years that it would take to measure whether or not this improved their lifetime health.

Imagine the entire population is sequenced and we race into developing precision medicines for each individual. How precise can precision medicine be? And can the people who contributed their genomic information receive the treatment as a benefit? That is unlikely right now. Donors are likely to benefit the future medical advancement and human population as a whole, but only a few can receive direct benefit. But if the whole cycle gains momentum, more people can receive direct treatment benefit before their disease becomes uncontrollable.
ARE WE READY?
IS OUR HEALTHCARE SYSTEM READY FOR GENOMICS?

The healthcare is not ready for genomics yet because of the vast quantity of genomics data, velocity of corresponding precision medicine development, health infrastructure, etc. Converting integrated imaging, pathology and genomic data into clinically actionable information is a daunting task. That includes electronic medical record systems that aren’t designed to deal with rich information, such as DNA, images and pathology, and the complexity of decoding and annotating the genomic information. There is also the challenge of physicians who would need further genetic training and ensuring they can keep up with the pace of publications of clinical research with genomic components – currently thousands each week in cancer alone.

Ethics and legal constraints also need to be added to the equation. We as a human beings have not quite figured out what to do with genomics, what is right or wrong, what will be done once we know our/others’ genomic information. Regulators are uncertain about the definite response to this topic as well. Just like driverless cars, before we decide on a devastating situation of whether to hit the train or run over a child, then ask programmers to program the standard ethics in the car, it will not become mainstream to mix with driver-driven cars on the same road.

There’s plenty of interest and we see the possibilities, but application of genomics in healthcare today is restricted to early adopters. While genomics is picking up quickly, disease by disease, for it to become a truly mainstream option it will need to be tied into the everyday practices of healthcare: based on integrated patient data, embedded into clinical pathways, and supported by real-world evidence and reimbursement models.

Though challenging, these barriers are not insurmountable, and they are already being tackled by initiatives in advanced diagnostic centers around the world. With today’s digital and connected technologies we have great opportunities to translate genomics into widely applicable, validated clinical practice.

WHAT WILL THE FUTURE BE?

We are not yet at the point where a healthy patient walks into a doctor’s office and arranges to have her genome sequenced to scout for potential future problems, then our doctor can present a precision medicine tailored for each of us and solve our problems without any considerations and restrictions. But this is the direction we are heading or want to, head and it won’t take long.

Lisa Stump, CIO at Yale New Haven Health Systems, suggested that in the not-so-distant future newborns will have their entire genomes mapped: “It will become as routine as other data points we capture, like a child’s growth chart.”

If a crystal ball tells our future, will everybody queuing up look into it? If we lack the means of changing the future if a negative event is around the corner, or a joyful surprise waiting for us, will knowing them makes us depressed or spoil the surprise?

We are moving forward under the assumption that an individual’s genome sequence is fundamental medical information, which will not explain everything about a person’s illnesses and risks but can explain a lot now and more in the future. A rough draft of the human genome was first completed by the Human Genome Project in early 2001. It is 16 years later and we’re in the middle of a genomic revolution. It might be less than 16 years before understanding of our code of life will be an integral part of
medical practice and help us live longer and healthier lives. A decade from now, we expect doctors to have ready access to their patients’ genetic information in routine care settings where medicine will be truly personalized.  

To make any of this possible, the next steps involve making genome sequencing and analysis routine; implanting genomics in current reimbursement models; encouraging larger, more comprehensive studies; addressing fears about privacy; convincing people to take the plunge and find out what their genes hold in store; and larger humanitarian consultation on what we shall handle genomic information and being prepared for its consequences on the individual and population level. This won’t be accomplished overnight – not everyone will want to know about their predisposition for contracting an illness that the medical industry of the day can do little about (e.g., Alzheimer’s) – but for many of us, it could well be the case that forewarned is forearmed. Prevention and early intervention have a big impact on health outcomes.
5. https://www.genomicsengland.co.uk/the-100000-genomes-project/
7. https://www.23andme.com/
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