How to make personal genomics mainstream: Crossing the chasm

Georges Nabaa

Email: nabaa@stanford.edu

Biochem 158

Written under the guidance of Professor Doug Brutlag

June 7th, 2013

Table of Contents

1 Introduction

Personal genomics holds the key to our genetic make-up and the promise of better health. However, the technology has not been able to cross the market chasm beyond niche early adopters and ancestry hobbyists. Even market leader 23andme has struggled to reach the 1M subscribers mark in a green field market.[1]

According to a paper by Khoury et Al. endorsed by the CDC, "the clinical validity and utility of personal genomics is a moving target with rapidly developing discoveries but little translation research to close the gap between discoveries and health impact."[2] A closer look at personal genomics reveals a slew of challenges that range from technical to public perception that are hindering the adoption of this promising technology.

In this paper, we explore the promises and current limitations of personal genomics and propose a possible path that allows the technology to become a mainstream staple.

2 The Promise of Personal Genomics

In order to build a product around personal genomics, it is helpful to first understand the potential benefits of the technology from a patient's standpoint. The CDC study[2] breaks down these benefits into four buckets of health improvement impact based on the stage of the disease.

2.1 Identifying Disease susceptibility

The primary bucket applies to genomic information that can lead to "a reduction in the disease incidence" by identifying the risk of contracting a given ailment such as type 2 diabetes. In this instance, personal genomics "may inform decision making for minimizing risk exposures, improving health

[1] http://blog.23andme.com/news/one-million-strong-a-note-from-23andmes-anne-wojcicki/
[2] Khoury, Muin J., et al. "The scientific foundation for personal genomics: recommendations from a National Institutes of Health–Centers for Disease Control and Prevention multidisciplinary workshop." *Genetics in Medicine* 11.8 (2010): 559-567

behaviors and lifestyle factors, or providing prophylactic surgery, chemoprevention, or other customized interventions." [2]

Table 1 Potential uses of personal genomics to improve health, in relation to stages of disease prevention and therapy[a]

Potential use of personal genomics to improve health	Description	Examples
Primary prevention	Testing that leads to reduction of disease incidence	Testing for susceptibility to cancer, type 2 diabetes, coronary heart disease to target interventions (e.g., cholesterol reduction, weight loss, chemoprevention)
Secondary prevention	Testing that leads to early disease detection and interventions	Testing for susceptibility to prostate cancer, and colorectal cancer (e.g., targeted screening)
Tertiary prevention	Testing that leads to personalized treatments (e.g., pharmacogenomics)	Testing for susceptibility to drug reactions and effectiveness (e.g., warfarin, SSRIs)
Quaternary prevention	Testing that leads to patients' improved quality of life, psychosocial effects, palliative care, etc.	Testing for susceptibility to diseases, with no available interventions (e.g., Alzheimer disease)

[a]There are other terminologies used for stages of prevention (e.g., primordial prevention in heart disease). The stages presented here apply to cancer and other common chronic diseases and are elaborated on by Miller et al.[11]

2.2 Pharmacogenomics

Pharmacogenomics, -the ability to match an individual's genetic profile to the likely effect of particular drugs [3] - , is another key benefit of personal genomics (tertiary bucket as classified by the CDC). The variability in drug response has led the "Food and Drug Administration (FDA) to alter drug labels and issue warnings"[4] in a way that integrates pharmacogenomics. Notable examples where pharmacogenics tests are widely used:

- Cardiovascular drugs "have narrow therapeutic indexes that are influenced by genetic variation"[4] which makes them prime candidate for reaping the benefits of this technology. In fact, response to Warfarin – one the leading drugs for treating cardiovascular disease- has such a wide response spectrum that it is "one of the drugs most often responsible for emergency room visits"[4]. This fact has not been lost on the FDA which "revised the label on warfarin in

[3] Hudson, Kathy L. "Genomics, health care, and society." *New England Journal of Medicine* 365.11 (2011): 1033-1041.
[4] Wang, Liewei, Howard L. McLeod, and Richard M. Weinshilboum. "Genomics and drug response." *The New England journal of medicine* 364.12 (2011): 1144.

February 2010, providing genotype-specific ranges of doses and suggesting that genotypes be taken into consideration when the drug is prescribed"[4]

- Analgesics, Antiarrhythmics, Antifungals, Antiinfectives, Antivirals, Gastroenterology, Hematology, Neurology and Psychiatry drugs also strongly benefit from pharmacogenics (According to a very detailed resource by the FDA[5])

3 Market Hurdles

3.1 Technology limitations:

3.1.1 Causality versus correlation

Genome wide association studies (GWAS) report statistical correlation of a disease against specific genetic marker areas. However, "Just because an association between genetic variation and disease is statistically significant does not mean that it is clinically meaningful"[6].

Moreover, the causality vs. correlation subtlety is lost even among risk and portfolio management professionals: Goto et Al list the causality-correlation confusion as one the most common psychological biases that lead to "Faulty human judgment in decision-making under uncertainty"[7]

In fact, personal genomics in its current incarnation faces an uphill battle, with its inability to deliver on lofty market expectations created by centuries of single-factorial mendelian diseases and popularized in science-fiction movies such as Gattaca. "Notions of genetic determinism have also been eroded as population genomics research has discovered a plethora of risk factors that offer only probabilistic value for predicting disease"[8]

---

[5] http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
[6] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2220016/#R2
[7] Goto, Shigeyuki. "The bounds of classical risk management and the importance of a behavioral approach." *Risk Management and Insurance Review* 10.2 (2007): 267-282.
[8] Knoppers, Bartha Maria. "Consent to 'personal'genomics and privacy." *EMBO reports* 11.6 (2010): 416-419.

3.1.2 Lack of marker applicability for all ethnic groups

Another limitation surrounding personal genomics is that a large number of the genome wide association studies (GWAS) have been completed for specific ethnic groups (usually European ancestry). Conclusions based on a given group are generally not applicable to other groups. As an example, studies of Behcet's disease,- a rare auto-immune disease that impacts individuals in the middle-east and Japan- reveal different genetic markers for both groups.

3.1.3 Limited actionable results

GWAS "are invaluable for understanding disease pathogenesis, but the present utility of this information for making treatment decisions is limited." What does a slightly elevated risk for a disease imply? When does a patient become alarmed? In fact, there is no common agreement around the statistical significance requirements for the results of a genetic test to warrant an action from a health care provider.

3.2 Privacy and Ethical Concerns

3.2.1 Complicated Terms of service

23andme's –the leading genomics provider- terms of service reads 8890 words and close to 123 paragraphs. Navigenics[9] does slightly better at about 55 paragraphs. However, both popular services miss the mark in terms of creating a simple message around user privacy. Maintaining patient privacy – a tenet of medical research- has become increasingly difficult with the advent of sophisticated data mining techniques. These techniques rely on actively sifting through multiple disparate datasets to reconstruct and identify the anonymized data fields. For example, publicly available anonymsed datasets, "such as voter registration or […] census data […] can be used in combination with other data sources to reidentify individuals in specific data sets". This has led the NIH to "remove open web access

[9] https://www.navigenics.com/visitor/policies/our_policies/terms_conditions/

to genomic datasets after it was demonstrated that individuals could be re-identified from aggregated data on genome-wide association studies and that therefore the removal of identifying variables or the publishing of aggregate data alone were insufficient to protect the privacy of research participants"[10].

The result of the two trends is an environment where "the participant may be unaware that their DNA is part of a collection being used for genomic research let alone the privacy implications of its release and reuse".

Finally, the Genetic Information Nondiscrimination Act (GINA) of 2008 which aims to "protect consumers from discrimination by health insurers and employers on the basis of genetic information"[11] falls short in terms of re-establishing consumer confidence in case a data breach occurs. GINA glaringly "does not cover life, disability, or long-term-care insurance"[12].

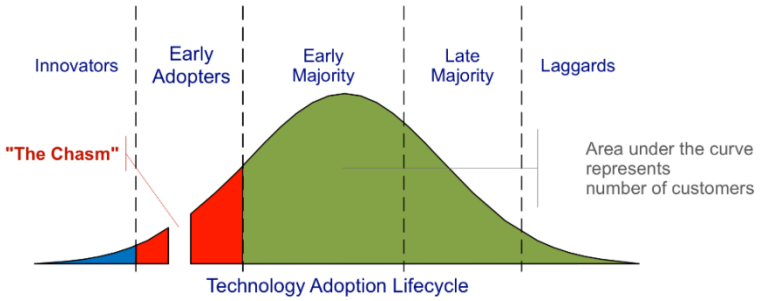
3.2.2 Ethical dilemmas

A number of ethical dilemmas surrounding personal genomics have been raised. Genetic testing for debilitating diseases that have no cure such as Alzheimer is a hotly debated topic. In fact, for the APOE Alzheimer marker, the test "is not currently recommended for asymptomatic persons"[13]. Research has found that "Knowledge of the results of genetic-susceptibility testing may cause anxiety, depression, and other types of distress"[13]

[10] Heeney, C., et al. "Assessing the privacy risks of data sharing in genomics."*Public Health Genomics* 14.1 (2010): 17-25.
[11] Hudson, Kathy L., M. K. Holohan, and Francis S. Collins. "Keeping pace with the times—the Genetic Information Nondiscrimination Act of 2008." *New England Journal of Medicine* 358.25 (2008): 2661-2663.
[12] Hudson, Kathy L., M. K. Holohan, and Francis S. Collins. "Keeping pace with the times—the Genetic Information Nondiscrimination Act of 2008." *New England Journal of Medicine* 358.25 (2008): 2661-2663.
[13] Green, Robert C., et al. "Disclosure of APOE genotype for risk of Alzheimer's disease." *New England Journal of Medicine* 361.3 (2009): 245-254.

4 How to cross the chasm

In 1991, Geoffrey Moore segmented the market according to the technology adoption lifecycle (See image below) . He penned the success of a startup upon its ability to “cross the chasm” from innovators to early adopters to early majority. The book is now a perennial reference and a must-read for product managers.



Personal genomics is in the midst of crossing the chasm with market leader 23andme aiming to reach its millionth worldwide subscriber. The next sections provide a few key recommendations to help reach this goal.

4.1 Improve Market Awareness

Personal genomics suffers from a lack of public awareness and needs to fix its branding. High-profile brand ambassadors such as Angelina Jolie which “underwent a preventive double mastectomy after learning that she carries a mutation of the BRCA1 gene”[14] are critical towards reaching this goal. In fact, by deciding to discuss her mastectomy in a public forum, Jolie “instantly created global awareness for genetic screening and preemptive medical procedures.”[14] Moreover, companies operating in this space should address patient privacy concerns more explicitly by simplifying the message around the terms of service. This last step is paramount to creating trust in a mainstream user base.

[14] http://www.cnn.com/2013/05/14/showbiz/angelina-jolie-double-mastectomy

4.2 Simplify the results

As discussed in section 3.1.1, even seasoned risk management professionals have a hard time understanding and making objective unbiased decisions based on correlations. The table below which captures the results from a Navigenics test result does not make use of this fact, since it provides up to 6 statistical parameters to capture a disease risk index[15]. Even in the presence of a genetic counselor, such an esoteric presentation is bound to alienate a mainstream user base. Instead, it is probably advisable to choose a single proxy value backed by strong visuals to represent the disease risk index.

Table 1. Risk Index Provided to Study Subjects by Navigenics and Composite Risk Analysis Variables.*

Variable	Definition
Risk index	
Estimated lifetime risk	A subject's estimated lifetime risk of a particular condition, expressed as a percentage (i.e., the risk of the condition among persons of the same sex over an average life span); if a subject's estimated lifetime risk was more than 80%, ">80%" was the result provided to the subject rather than the actual estimate
Average lifetime risk	The average sex-specific lifetime risk in the population for a particular condition, expressed as a percentage
Percentile floor	Percent of HapMap CEU reference subjects with a lower genetic risk than the study subject
Percentile ceiling	Percent of HapMap CEU reference subjects with a higher genetic risk than the study subject
Dashboard color	Color-coded risk, with orange indicating either an overall lifetime risk of more than 25% or a risk that is more than 20% above average and gray indicating low risk
Composite risk analysis variables	
Total no. of conditions viewed	Total number of conditions the subject viewed out of 22 possible conditions (with breast and prostate cancer provided on a sex-specific basis)
Individual average estimated lifetime risk	Average estimated lifetime risk for all conditions that the subject viewed
Individual proportion of orange-coded conditions	Number of conditions for which the subject received a high-risk color code divided by the number of conditions viewed
Individual highest estimated lifetime risk	Highest estimated lifetime risk the subject viewed

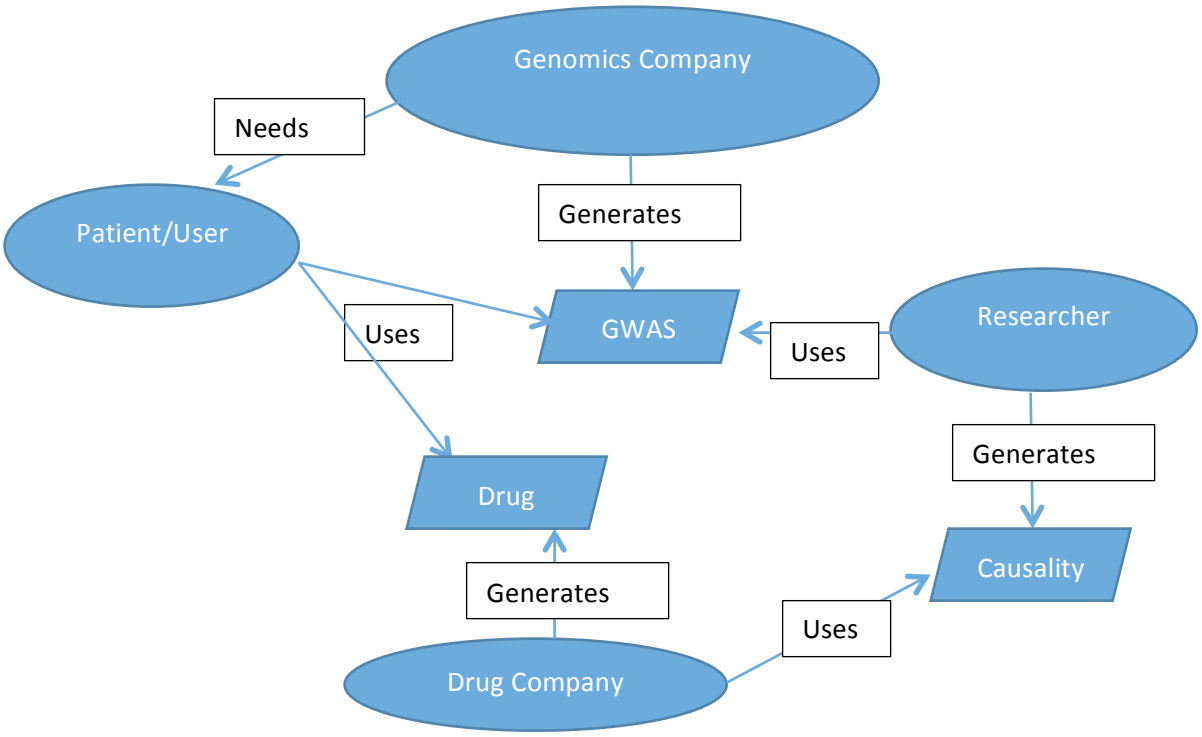
* CEU denotes Utah residents with ancestry from northern and western Europe in the data set of the Centre d'Etude du Polymorphisme Humain.

4.3 Create a solution around the complete ecosystem

The current genomics ecosystem is driven by the following stakeholders: patients, health care providers, pharmaceutical companies, genomics companies and genetic researchers. So far, the two leading

[15] Bloss CS et al. N Engl J Med 2011;364:524-534.

companies have approached their business models very differently[16]: 23andme markets directly to consumers while navigenics forces the user to go through their health provider.



The graph above attempts to depict pictorially the relationship between the different stakeholders. At the base of it all is the end-user which holds the data required for the entire ecosystem. Genomics companies need this data to perform their GWAS studies. These are then utilized by the genetic researcher to further investigate and understand the causality of a given disease. The causality finding is then used by the drug companies to come up with a treatment. We finally come back full-circle to the patient which uses the drug results or the GWAS to improve his/her health.

By visualizing the value chain, one can infer that the genomic offering that will cross the chasm will have to successfully incorporate all these stakeholders in its business model. A possible model would place

[16] http://www.nytimes.com/2010/03/20/business/20consumergenebar.html?_r=0

the monetization burden downstream from the patient/end-user as an incentive to fast-tracking the genetic and phenotypic data required by GWAS.

5 Conclusion

In this paper, we proposed a set of recommendations to enable personal genomics to become a mainstream technology. The recommendations draw on the benefits offered and help rectify the limitations of personal genomics. We presented improved health outcomes at different stages of disease prevention and pharmacogenomics as two clear benefits of personal genomics. We also explored the lack of marker applicability for large ethnics groups, the limited actionable results and the privacy and ethical Concerns as main limitations of the technology.

In order to help personal genomics cross the chasm, we suggested 1) improving market awareness, 2) simplifying the offering and 3) creating a complete solution that encompasses all the stakeholders in the ecosystem. We also suggested a monetization strategy away downstream from the consumer since his genetic data is the basis of the whole ecosystem.