Unlocking the Power of Your Genome: Financial and Regulatory Challenges

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ABSTRACT

This thesis examines the greatest obstacles to translating genomics research into the clinic and market: lack of reimbursement and regulatory uncertainty. I examine three companies and how their business models address those challenges, as well as the role of legislation, specifically the proposed Genomics and Personalized Medicine Act. By analyzing 23andMe's direct-to-consumer approach, Navigenics' facilitated model (whereby services are offered through physicians), and Genomic Health's "pharma approach" to molecular diagnostics (in which clinical validation is key to reimbursement), I found that the various business models audiences may have a synergistic effect in bringing genomics into clinical use. The eventual success of a particular model will be determined by public perception of patients' relationships to genomics. Furthermore, GPMA proposed measures may successfully address regulatory challenges by centralizing efforts. Finally, while reimbursement challenges can be alleviated through legislation providing financial incentives, some difficulty in achieving insurance coverage is appropriate due to the importance of ensuring that genomic products are rigorous, preserving industry integrity, and maintaining cost-effectiveness. Through the focus on the financial and regulatory challenges faced by industry, this thesis contributes to the growing body of research which aims to clarify the path to realizing genomics in the clinic.

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INTRODUCTION

Thirty years after the discovery of DNA's double helix structure, the scientific community had begun setting its sights on a new goal: the full sequence of the human genome. The public and media referred to the Human Genome Project (HGP) alternately as the "holy grail of biology," the "book of man," or the "blueprint for all life." The project was compared in scale and grandeur to the Apollo mission to the moon or the Manhattan Project, and was characterized by Congressional testimony as a "turning point" in the battle against cancer and AIDS.[1] With the stakes so high, Congress approved the $3 billion budget over a 15-year period to sequence the human genome, and work began in 1990. By 2000, a first draft of the genome was complete, five years early and $300 million under budget.[2]

Since the completion of HGP, sequencing technology has rapidly become more efficient, in terms of both time and cost, and more than 60 individuals' genomes have been made publicly available. Life Technologies announced that by the end of 2012, it will launch a machine to sequence a human genome in a few hours for $1000.[3] These technological developments in genomics have people talking about ushering in the age of personalized medicine—collecting more and more information about individual patients so that their diagnostics and treatment is personalized to them. Several companies such as 23andMe and Navigenics already offer services for interpreting consumers' personal genomics (based on thousands of genetic variations rather than the entire genome). While sequencing technology has even outstripped Moore's Law (an

[1] Allender-Hagedorn, 2001.

[2] NHGRI, FAQ.

[3] Herper, 2012.

exponential growth law describing the limits for developments in electronics)[4], researchers are making strides in bioinformatics to interpret the vast amounts of genetic information available: from pinpointing drug dosages to evaluating cancer therapies. However, despite the tremendous amount of research being undertaken in many aspects of personalized medicine, these new findings are not being fully utilized in clinical settings.

Though the scientific achievement in itself of genome sequencing was important and impressive, much of the incentive for this research was not solely understanding, but also its relevance and application to healthcare. Many questions remain about how to put this research best to use. Some have called personal genomics recreational and interesting, rather than useful.[5] Others argue the information could even be harmful, especially in light of privacy issues, concerns of increased insurance costs, and lack of counseling for patients given genetic testing results.[6] Finally, some continue to see the potential of genomics to transform healthcare as we know it and have called for policymakers to put in place the regulatory and financial systems in place to support personalized medicine.[7]

Despite these high expectations for the transformative power of this field for medicine and health, genomics has not yet been incorporated into routine clinical practice on a wide scale. In this paper, I will discuss the challenges in translating this research into an improvement in the current standard of care: primarily lack of reimbursement by third-party payers as well as lack of clarity and guidelines from regulatory agencies.

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[4] NHGRI, Sequencing Costs.

[5] Ormond et al., 2011.

[6] Ransohoff & Khoury, 2010.

[7] Personalized Medicine Coalition, 2012.

BACKGROUND

The Science: What is DNA?

To understand the technological significance of genomics and fully appreciate the debate, it may be helpful to understand what DNA is made up of and its importance to living organisms. DNA, or deoxyribonucleic acid, is made up of two complementary strands of repeating units called nucleotides. These nucleotides are molecules which come in four types for DNA: adenine (A), cytosine (C), guanine (G), and thymine (T). As the two strands of DNA complement each other, each nucleotide (or base) has a pair in the opposite strand: A bonds with T, while C bonds with G. Thus, all the information on one strand is contained in the complementary strand as well, but in the opposite direction, as shown in Figure 1 below.

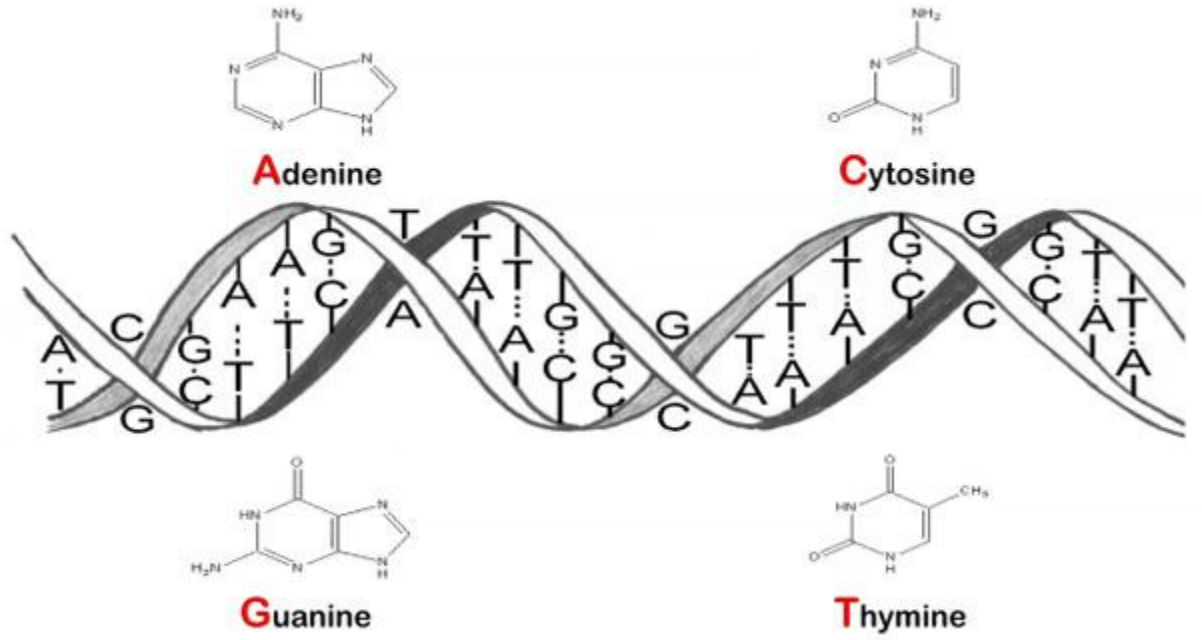

Figure 1, from "Welcome to the Genomics Revolution" by R. Resnick, 2011, TEDxBoston

A stretch of nucleotides that has a function in the organism is referred to as a gene. The entire human genome, or the collection of all of a person's genes, is made up of six billion base pairs. Some of these genes have known functions and phenotypes (observable physical and behavioral characteristics of an organism): for example, both cystic fibrosis and Huntington's disease each can be identified by presence of a mutation in a single gene.[8] However, many phenotypes are more complex and are determined by multiple different genes as well as external factors, and not all of this information is yet known.

How exactly does a gene influence a phenotype, or rather how do these genes become expressed? DNA is transcribed to RNA, which carries the genetic information, and RNA is translated into proteins. These proteins serve many functions within the cell and the human body: they can protect (as antibodies), transport, store, provide structure, signal cellular activities, catalyze reactions, and execute the transcription and translation processes themselves. Thus, the genetic code, which is made up of four bases and can be read out as a simple (but long) sequence such as "…ACTGGTACGC…," is responsible for incredible complexity, governing cellular functions in every tissue within every organ of the human body. This flow of genetic information described is called the "Central Dogma of Molecular Biology," which is summarized in Figure 2 on the following page.

[8] Chial, 2008.

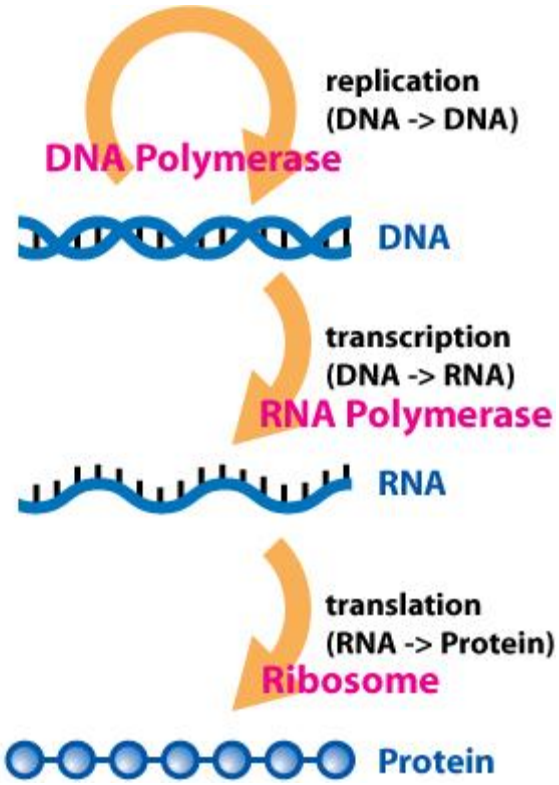

Figure 2, by D. Horspool, 2008, Wikimedia Commons

The contribution of each parent's genes to the child's DNA should also be noted. DNA is organized into structures called chromosomes. Human beings are diploid, meaning that they have two copies of each of their 23 chromosomes. One copy is inherited from the mother, and another copy is inherited from the father. For any given gene, a person might have two of the same allele (or variations in genes) or two different alleles, one from each parent in both cases. The significance of each allele can vary greatly depending on the gene. Additionally, the difference between a gene's alleles can be as small as a single nucleotide; this variation is termed a SNP, or single nucleotide polymorphism.

In some cases where phenotype is the result of a single gene, for example with Huntington's disease, having just one of the two alleles for that gene is enough to assert a

specific phenotype; the asserted allele is called autosomal dominant. In other cases involving a single gene, a phenotype will only be exhibited if both copies of the gene have the specified allele, in which the particular allele is termed autosomal recessive, as with sickle cell anemia or cystic fibrosis. There are also situations where one or both copies of a gene are deleted, where one or both copies are mutants with no function, or where the number of times a particular region is repeated within the gene changes the phenotype. Each of these circumstances has a varying relationship with the expressed phenotype and can be very complex. Furthermore, environmental conditions and multiple genes (rather than a single gene) are often involved, as is the case for most common diseases such as diabetes, stroke, heart disease, and many different types of cancer. This increases the complexity of the causal relationship between genotypes and phenotypes.

Because genetics are inherited, family history is often an excellent predictor of disease, and it is commonly used in studies of genetic disease. However, family medical history is typically not well documented, and responsibility falls upon the patient and their family to collect accurate information. Even with a detailed family history, in many cases, it is impossible to know with certainty about inherited genetic diseases without having a genetic test done.

Though genetic tests can confirm, rule out, or predict some diseases, many genetic causes of disease are still unknown, and the function of most of the genome remains a mystery. As such, genomics enthusiasts see genome interpretation and discovery of gene function as an enormous untapped potential for disease prevention and treatment. Theoretically, it could enable the practice of truly preventative medicine, tailored to each individual, based on genetic

evidence rather than the current state of healthcare in which physicians must wait for symptoms in order to treat medical problems.

The Technology: Sequencing and Bioinformatics

With sequencing costs and processing time dropping rapidly with new technologies, sequencing difficulties will soon no longer be a limiting factor in genomics-based personalized medicine. In fact, corporate executives expect the reduced cost to allow researchers to expand their sample sizes and "drive further adoption of whole-genome sequencing as the preferred method for assessing variation across genomes."[9] Thus, the increased accessibility of sequencing technology, in addition to making clinical use of sequencing more feasible, could potentially increase the volume of bioinformatics research and accordingly scientific knowledge and understanding of the genome as a whole, thereby feeding back into the utility of sequencing in clinical practice in terms of interpretation.

In light of the expense and sheer volume of information associated with whole genome sequencing, one might wonder how bioinformatics research is conducted without studying entire genomes. One massive data source is DNA microarrays, which can provide data for up to one million base pairs.[10] However, whole genome sequencing gives six billion base pairs, and thus 6,000 times more data as a microarray can. The limitation of microarrays can also be an

[9] BusinessWire, 2011.

[10] UCSF Gladstone Institutes.

advantage as researchers can avoid shooting in the dark and do a more focused and rigorous study. Also, less data will require less storage and memory.

Bioinformatics research has led to some fascinating findings: applications primarily relate to diagnostics and treatment, that is the genetic predisposition towards disease as well as the genetic basis of drug response. Initially, primary methods of investigation included inheritance studies of genetic linkage in families, which was useful for single-gene disorders. In 2005, genome wide association studies (GWAS) were introduced and gained popularity as a method of understanding genetic associations with complex diseases. However, some academics have claimed that GWAS will no longer provide results to justify the costs. Critics have also questioned the value of GWAS as it is difficult to differentiate between causal variants, or variations in DNA that cause disease, and simply genes that are correlated indirectly with the disease. Finally, because there are so many genes that contribute to complex disease, identifying only a few variants may not be so useful.[11] Other methods and applications of bioinformatics have become more prevalent instead. For example, methods of mining electronic medical records (EMR) to uncover correlations between genetics and disease[12] or to uncover drug-drug interactions[13] are gaining popularity. Also, the use of genetics to better recommend cancer treatment has been an exciting area of oncological research: if researchers can understand what genes make certain cancer cells resistant to therapy through analysis of cancer recurrence and patient survival, they are better equipped to treat the cancer without a relapse. There is a wealth

[11] Wade, 2009.

[12] Ritchie et al., 2010.

[13] Tatonetti et al., 2011.

of microarray data of tumor samples publicly available, which has much more potential for further analysis beyond their use in previous studies.

With new developments in research methods, data sources, and applications occurring at a very high rate, many argue that the promise of bioinformatics research remains full. It appears that translating these research findings into clinical practice is as relevant as ever.

Highlights in Clinical Research

In 2010, Stanford researchers conducted the first integrated analysis of a complete human genome, that of Professor Steve Quake, in a clinical context. They assessed Quake's risk for coronary artery disease and sudden cardiac death in particular due to his family history. He was found to be at increased risk for myocardial infarction, type II diabetes, and certain cancers. Analysis also showed an expectation for a good response to statins, a drug that lowers cholesterol.[14] Normally, physicians would take a "watch-and-wait approach" before prescribing drugs, but given the patient's lifetime genetic risk for heart disease as well as his likely positive response to statins, cardiologist Dr. Ashley, the first author of the paper, recommended Quake consider taking the statins immediately rather than wait for symptoms.[15]

A more recent case of Stanford genomics research contributing directly to personalized medicine was published in Cell in March 2012: Mike Snyder, Genetics chair, was the subject of biological profiling for more than two years. Snyder's genome was mapped, and his team of geneticists reported all the proteins in his body, in addition to other molecular data, at specific

[14] Ashley et al., 2010.

[15] Conger, 2010.

points in time, a collection of data that the researchers call the "integrative personal omics profile," or iPOP while others have nicknamed it the "Snyderome" and even the "narcissome."[16] His genomic profile revealed a predisposition towards type II diabetes, which was a surprise due to lack of family history of diabetes, and halfway through the study, a molecular snapshot found that his body was not regulating glucose normally followed by a later snapshot showing a spike in insulin.[17] A doctor's visit confirmed the onset of diabetes, and Snyder began making changes to avoid diabetes medications. When Snyder went to get a glucose metabolism test to confirm suspicions from his research, he was told, "There's no way you have diabetes."[18] Snyder claims that without this study, he would not have been diagnosed for another year or two.[19]

Both of these studies show the power of genomics to affect medical practices on a case by case basis, especially for early prevention and treatment of disease. Without this research, it may have been years before the patients and their doctors took steps to address these issues. With such powerful examples of personalized medicine research, many questions remain. Will this type of research be useful to most patients? If so, how can we develop this practice on a wider scale? And perhaps most relevant to this discussion, what role do legislators and corporations play in addressing these challenges, and accordingly what business models and laws are most effective or perhaps necessary to reap the benefits to the public of genomics and personalized medicine?

[16] Dennis, 2012.

[17] Allday, 2012.

[18] Cohen, 2012.

[19] Conger, 2012.

While these research studies provide convincing narratives in favor of using genomics to personalize medicine, skepticism over the utility of genomics continues. For example, some point out that while Quake's cardiologist prescribed statins, Quake himself has refused them. Furthermore, some question whether the findings thus far are the "tip of the iceberg or the bottom of the barrel."[20] One study examining identical twins (who therefore have identical genomes) has gained a large amount of media attention, including featured coverage in the New York Times. The study looked at twins' medical histories and concluded that most common diseases cannot be predicted based on genetics: it claims "the majority of tested individuals would receive negative tests for most diseases" despite the fact that these individuals' risk for that disease would likely mirror the general population's risk. On the other hand, the research also concluded that "in the best-case scenario, the majority of patients might be alerted to a clinically meaningful risk for at least one disease" and that genetic tests are likely to identify 75% of patients who eventually develop thyroid autoimmunity, type I diabetes, Alzheimer's, and coronary heart disease.[21] This publication essentially warned of the limited capacity of genomics to predict disease, drawing criticism that the study does not actually use genomic data, does not account for errors that can affect twin studies, and for the mistaken assumption that proponents of genomics believe in genetic determinism.[22] It nevertheless offers an alternative scientific narrative for the predictive capacity of genomics, which can be useful if read critically.

While academics debate the clinical utility of full genome sequencing by using individual cases and statistical models, several initiatives are underway to assess the utility on a wider scale

[20] Iles, 2008.

[21] Roberts et al., 2012.

[22] Hayden, 2012b.

by actually implementing personal genomics in the clinic. The Corielle Personalized Medicine Collaborative, which began in 2007, explores the use of genomic information in clinical decision-making by genotyping volunteers and partnering with doctors, hospitals, scientists, genetic counselors, and IT experts in order to examine multiple aspects of the technology in the healthcare setting.[23] The Mayo Clinic, a hospital known for its research and integrated care, has also announced that it will launch a pilot study this year where thousands of volunteers will have their genomes sequenced and "linked to their medical records to help doctors prescribe more effective drugs and therapies."[24] The Corielle Personalized Medicine Initiative and Mayo Clinic pilot study may be the most definitive and influential in understanding the limitations and power of personal genomics in the clinic because of their wide scale and integrative approach.

Commercialization of Genomics

With genomics and bioinformatics research blossoming in academia, many companies have risen to the challenge of commercializing these findings as well as accelerating research and development in a fast-paced, corporate context. As shown in the graphic on the following page, enterprises are entering several different market spaces within the genomics industry. For example, several companies are taking part in the race to be the first to offer the most cost-effective and efficient sequencing technology. This competition has been marked by friendly and unfriendly acquisition attempts: Swiss pharma giant Roche acquired 454 in 2007 and

[23] Coriell Institute for Medical Research.

[24] Sample, 2011.

attempted a hostile takeover bid of Illumina in 2012 as well, while Life Technologies acquired Ion Torrent (founded by Rothberg, who also founded 454) in 2010.[25]

Figure 3: Various Sectors and Companies within Genomics Industry

Another market space, which has received quite a bit of media attention, is that of genomic interpretation. The business models and target consumers of these companies vary with the degree to which they aim to be incorporated into clinical practice, which will be discussed in the case study portion of this thesis. There are also companies that create software tools and products to assist researchers with analysis of large quantities of genomic data, companies that are creating diagnostic genetic tests, and companies that specialize in a particular aspect of genomics and health such as the immune system or cancer profiling or even the Gattaca-evoking sphere of involving genomics in pregnancy planning.

[25] Hayden, 2012a.

Current State of Government Involvement

Considering that the genomics industry and clinical trials are accelerating quickly, government legislation and involvement is a primary concern. As of today, there is little formal regulation of genomics and even genetics in general. Various bills relating to genetic discrimination were introduced in 1995; however, many iterations of the bill were introduced before the Genetic Information Non-Discrimination Act (GINA) was enacted in May of 2008.[26] GINA prohibits the use of genetic information for health insurance and employment purposes: health insurance companies cannot deny coverage or charge higher premiums solely based on genetic predisposition for disease, and employers likewise cannot use this information to make hiring, firing, job placement, or promotion decisions.[27] However, the clauses regarding insurance do not apply to life insurance or to long term care and disability insurance. Furthermore, the bill does not address privacy issues that may arise from direct-to-consumer (DTC) genetic testing, as many companies include contractual clauses that allow them to use and sell their clients' genetic information to third parties.[28] Finally, GINA does not address FDA regulation of genetic testing.[29] Noting that it took 13 years for Congress to pass the first piece of legislation regarding genetics, the Genomics and Personalized Medicine Act (GPMA), which has died after being introduced on four occasions, potentially has a long way to go.

One specific aspect of genomics which has seen a flurry of uncertainty in terms of commercial regulation has been the direct-to-consumer genetic testing industry. Regulation of

[26] NHGRI, Privacy and Discrimination Federal Legislation Archive.

[27] H.R. 493 (110th), 2008.

[28] Keim, 2008b.

[29] Keim, 2008a.

direct-to-consumer genetic testing products has been marked by a lack of Congressional legislation and industry-wide guidance, as well as what some view as unwarranted FDA aggression. Government involvement began in 2006 with the first Government Accountability Office (GAO) report and with the FDA, FTC, and CDC releasing a fact-sheet advising consumers to maintain skepticism about genomics. Congress also held a public hearing following a second GAO investigation in July 2010, while the FDA held a 2-day public panel in March of 2011. For a more complete timeline of government involvement in the DTC industry, see the figure in Appendix A.[30] The most tangible government action that has precipitated over the past six years is the FDA's practice of sending letter to DTC companies about their lack of clearance or approval, which is followed by initiations of private dialogues in order to determine company-specific regulation.

Finally, debates over the legitimacy of gene patents has made its way to the Supreme Court in the case of Prometheus, which may also have implications for the famous Myriad Genetics case. The company Prometheus held patents over the claim that there was a relationship between the levels of a specified metabolite and the efficacy or toxicity of drugs which treat gastrointestinal autoimmune disease. Mayo had at one point bought Prometheus's tests but eventually began selling and marketing their own similar test, at which point Prometheus sued for patent infringement. The case eventually reached the Supreme Court, which unanimously ruled that the patents were invalid because they essentially claimed unpatentable laws of nature, rather than the application of that law of nature by adding to the statement of correlation. Likewise, the famous case of Myriad Genetics, which patented the genes predicting heredity of breast cancer (BRCA1 and BRCA2), may be influenced in a lower

[30] Vorhaus, 2010.

court by the Supreme Court's ruling on patents regarding natural laws from the Prometheus vs. Mayo case.[31]

Lingering Questions about Genomics

In light of this background, many broad questions and debates have arisen in genomics. For example, the rightful ownership of genetic information still hangs in the air. Is every person entitled to their own genetic information? Is it overly paternalistic to require a genetic counselor or physician to interpret a person's data, or is it a necessary precaution to prevent potentially dangerous misuse of health information? Is a genetic test more like a home HIV or home pregnancy test, or is it comparable to an MRI or an X-Ray which must be ordered by a physician? Related to the rights of genetic information is the debate over gene patents: does the work to isolate DNA from the body transform it and make it patentable, or are genes fundamentally an un-patentable law of nature? And how will the answers to these questions affect the genomics industry and academic research, as well as the practice of medicine?

Another big issue bioinformatics faces is the deluge of data. Sequencing technology has developed to the point that the bottleneck is no longer obtaining new data, but rather having too much of it. The implications of this are deep and wide-ranging, as the data requires storage, transmission, and analysis—all of which requires time as well as money. It has been suggested that solutions to the data problem may come in the form of cloud computing, removal of "unnecessary" portions of the data, as well as hopeful innovations in bioinformatics

[31] Conley, 2012.

techniques.[32] Related to the flood of data, critics have claimed that the initial findings which had generated so much hype in genomics were just the "low-hanging fruit." They argue that amidst the six billion base pairs each from hundreds of individuals, additional important discoveries of the genetic bases of disease and treatment will be nearly impossible to make.

Finally, there is some debate over potentially creating a biobank of genetic information and the privacy and research implications of such an act.[33]

Financial Challenges of Implementing Clinical Use

The broader concerns discussed previously are huge questions in attempting to understand the future of genomics. These issues are all relevant to facing one of the biggest challenges of the implementation of genomics in the clinic today, which is the topic of this thesis: making genomics a financially viable option.

In light of the background covered, it is worth noting the complex relationship of the various players involved in implementing genomics in the clinic, including scientists, engineers, patent-holders, patients and consumers, physicians, genetic counselors, corporations, hospitals, insurance companies, various government agencies, and Congress. As a result, one of the primary issues facing clinical implementation is the navigation of these relationships to make this financially feasible and even desirable.[34]

[32] Pollack, 2012.

[33] Pulley, 2010.

[34] Gaalaas, 2012.

To introduce the details of this challenge, attention will focus on a favorite genomics case, warfarin. Two million new patients start warfarin every year in the US, in order to prevent blood clots. However, the appropriate dosage for each patient is difficult to pinpoint, with regular monitoring being necessary, and about 20% are hospitalized due to bleeding from over-anticoagulation.[35] Many studies have shown that pharmacogenetic testing could help estimate an appropriate dosage with greater accuracy than current methods. Nevertheless, in August of 2009, CMS said there was not enough evidence to support coverage of genetic testing to determine warfarin dosage without clinical data.[36] Furthermore, the testing results would not be returned quickly enough to influence dosage, and patients would still need monitoring. Clinical trials are currently underway, and one 2010 study showed that patients who underwent genetic testing before taking warfarin were about 30 percent less likely to be hospitalized.[37] The costs saved on hospitalization should theoretically compensate for the cost of genetic testing. However, at this point, alternative drugs have been introduced which are comparable to warfarin, without the same threat and inconvenience of dosage problems. A major theme noted from this example is that while an academic publication may present the power of genetic testing in drug dosages, testing would not be translated into the clinic until it could be reimbursed and have proven value. By the time trials were underway, many patients had to risk hospitalization from inappropriate dosages, and alternative drugs were proposed. The process of introducing genomics into the clinic appears slow and costly: investigating the obstacles to

[35] Kitzmiller, 2011.

[36] Pollack, 2009.

[37] American College of Cardiology, 2010.

this development, in the form of reimbursement and regulatory challenges in particular, is the focus of our discussion for this thesis.

METHODOLOGY

In order to examine the obstacles to bringing genomics to the clinic and market, my preliminary research included a literature review, some of which was described in the background section of this thesis. It also included informal conversations with individuals with a professional interest in genomics, either at Stanford University or at the Personalized Medicine World Conference 2012 which brought together academics, entrepreneurs, representatives from large corporations, physicians, venture capitalists, etc. This preliminary research allowed me to narrow my focus to addressing regulatory and financial challenges to translating genomics into the clinic and market.

With this focus in mind, I chose corporate case studies and policy analysis as appropriate methodology for qualitative research. By looking at individual companies, we can gain a deeper understanding of the challenges facing the translation of research into regular use and make broader claims about next steps or what the future of genomics beyond academia looks like.

To conduct the corporate case studies, I contacted about ten different companies in the genomics industry by e-mail, through my adviser Professor Altman's contacts, my personal contacts, and public information available on the company websites. I only contacted companies that were more involved with the interpretation and clinical aspects of genomics, rather than companies that developed sequencing technology or analysis software. Some representatives of these companies agreed to interviews, which were conducted at the interviewee's place of work and lasted approximately 40 minutes to an hour. Because the research topic was about the company rather than the individual being interviewed, I did not seek approval from Stanford Institutional Review Board (IRB), as my research did not qualify as

"human subjects research" by IRB guidelines. Interview questions are detailed in Appendix B, though not all questions are included based on the conversational nature of the interview (i.e., the actual interview included follow-up questions). Others responded that they did not have the resources to accommodate my request at this time, including a few who provided me with printed materials and information via e-mail to assist in my research.

The specific companies I chose to include in my case studies were chosen based on availability of information, either through printed materials or through interviews, as well as diversity of business models. In the case study portion, I describe each company's product, business model, and how they engaged with regulatory and reimbursement challenges. The contrast and similarities between these different approaches will be more useful for our discussion than several companies which operate in very similar ways.

For the policy analysis, I chose to examine the proposed Genomics and Personalized Medicine Act because of its relevance to the uncertain future of legislation. I evaluate the bill's provisions, taking into account public commentary and discussing advantages and disadvantages to each, especially with regards to regulation and reimbursement. I then make informed recommendations for the next iteration of the bill.

These two aspects of my research, in conjunction, will allow us to draw broader conclusions about widespread use of genomics and will inform a better understanding of policy's role in the "genomics revolution," which has through this point in time been described as uncertain and unclear.

CASE STUDIES

GENOMIC HEALTH

In 2006, Genomic Health, a company which uses genomic research for molecular diagnostics in order to personalize cancer treatment, was founded. Its first product, launched in early 2004, evaluated risk of breast cancer recurrence to inform treatment. Since then, Genomic Health has also introduced a product for colon cancer and is in the process of developing additional products for breast and colon cancer as well as products for prostate cancer, non-small cell lung cancer, renal cancer, and melanoma.[38]

The First Product

More than 100,000 patients were diagnosed with a particular form of breast cancer every year: early stage, lymph node-negative (N-), estrogen receptor positive (ER+). Patients typically had surgery and then had the option of undergoing chemotherapy treatment to decrease the probability of recurrence. Chemotherapy had some short-term side effects and potentially serious long-term implications, and clinical studies had shown that chemotherapy only improved survival rates by 4%. Nevertheless, many doctors recommended and patients chose the treatment, and many studies noted a "lack of consensus as to appropriate treatment for breast cancer coupled with a high confidence by individual clinicians in their own treatment decisions." Genomic Health's Onco*type* DX™ would use the genetic signature of the tumor to predict probability of recurrence and eventually to predict personal response to chemotherapy and tamoxifen. The results of this testing would thus inform and personalize treatment decisions for patients suffering from early-stage, N-, ER+ breast cancer: low-risk individuals could avoid

[38] www.genomichealth.com

harsh, unnecessary, and/or ineffective treatment options while high-risk patients would have peace of mind that they were making the right decision in undergoing chemotherapy. Furthermore, some patients might find that they are at higher risk than expected and therefore elect the chemotherapy treatment option when they might not have otherwise.[39] Though at first glance the translation of this technology into clinical use seems straightforward enough, reimbursement challenges and uncertainties of regulation complicate the company's pioneering search for an appropriate business model to implement the clinical translation.

Marketing & Demonstrating Value

Though Genomic Health was essentially aiming to deliver genomics-based diagnostics products, the company wanted to provide solution that were not just informative, but actionable – this would set it apart from other tests results like Myriad Genetics' testing. In order to do so, the products would require large expenses for research and development and thus would have to be priced high to support that R&D. In turn, in order to justify such a cost, Genomic Health would need to provide very compelling evidence of the value to all parties involved – physicians, patients, and payers – as well as others with credibility and power to influence decision-makers.[40]

The company took several steps to demonstrate value. First of all, Genomic Health decided to house its own testing and central reference laboratory, allowing them to maintain control over the product quality as well as pursue CLIA certification. Furthermore, while there was a small group of "early adoption"- minded physicians who perceived that the product could fulfill the need for molecular analysis to guide clinical decisions, most other physicians seemed

[39] Zenios, Chess, & Denend, 2006.

[40] Zenios, Chess, & Denend, 2006.

resistant to change, having used tumor size, tumor grade, and patient age to make breast cancer treatment decisions for years. Thus, though no regulatory body required clinical validation for diagnostics, the founding team discovered that many physicians would be reluctant to even consider a new approach without serious evidence that the test was clinically proven to work with certain utility. This finding confirmed that the use of clinical validation studies would be essential to their business plan, though it would increase the level of time and capital needed to bring the product to market. Finally, Genomic Health made a strategic decision about focusing on a single product first and chose breast cancer because of two of the founders' experience and network in the field. Founder Randy Scott said, "Steve [Shak, co-founder] had developed strong scientific relationships in the breast cancer field, and there was an enormous need in this area. There was also a huge advocacy community and we knew that anything we did in breast cancer would get enormous media attention, which potentially meant that our customers would support us in marketing the product."[41]

R&D and Validation Process

When the company's founders decided that clinical validation was essential to their business strategy (which is more typical of the pharmaceutical industry than diagnostics), they began to determine whether they could use archived breast cancer tissue samples in the R&D and validation process. Using archived tissue would allow the company to move fast in developing and testing new products, rather than waiting long periods of time to analyze recurrence outcomes. Thus, Genomic Health requested to secure small samples from the tumors as well as the associated clinical records for each patient, with the plan of analyzing

[41] Zenios, Chess, & Denend, 2006.

hundreds to thousands of genes concurrently to increase the odds of identifying the right genes for the test. Phase I of the process was to demonstrate that they could get meaningful signals from the archived samples, and Phase II would be to identify the specific genes of clinical interest. Eventually, the Oncotype DX™ product was able to predict the likelihood of breast cancer recurrence over 10 years based on the genetic makeup of the tumor with statistical significance. [42]

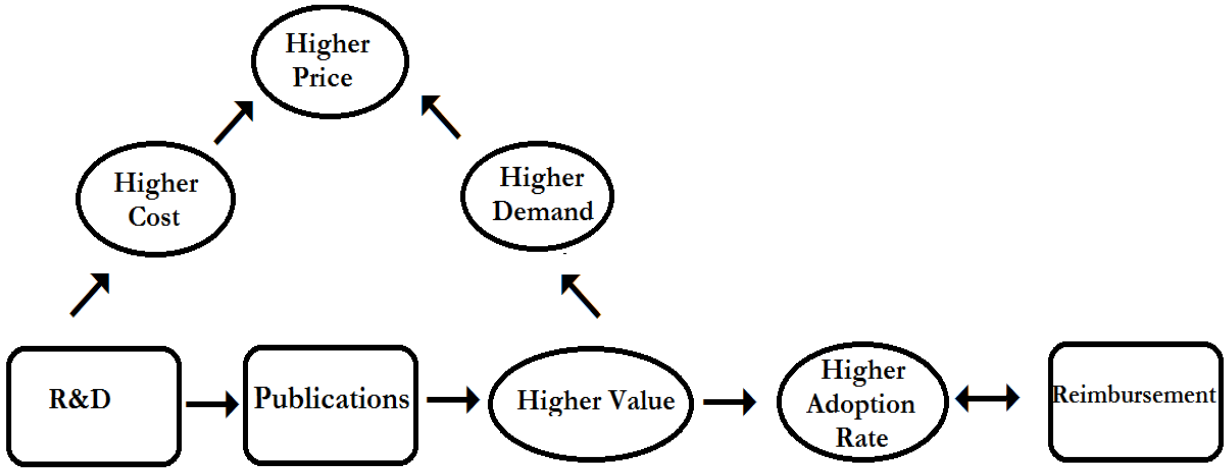

Figure 4: Graphical Representation of Genomic Health's Business Model

In the early stages of product development, feedback was generally that recurrence scores would be compelling enough to inspire physician interest in using the product. However, as the company neared the release of the first product, they said they began hearing from clinicians, "Even if patients have a low probability of recurrence, we're still going to give them chemotherapy if there's a chance they'll receive even a small benefit from it. So you need to tell us if patients are going to benefit from chemotherapy or not." So, even though the team believed it unlikely that low-risk patients would benefit from chemotherapy, they lacked critical data from initial trials and had to launch additional trials which would validate the product's

[42] Zenios, Chess, & Denend, 2006

ability to predict chemotherapy response. The team made the decision to execute additional trials, and within a year of the first product launch in early 2004, they had published data that the product could predict chemotherapy response in addition to likelihood of recurrence.[43]

It is also worth noting that Genomic Health chose to execute the trials in partnership with reputable, neutral third parties in the oncology field. This approach required significantly more time as the partners were responsible for publishing results, but it also increased the credibility substantially.

Reimbursement Strategy

As Genomic Health wanted to produce a test for clinical use, taking into account the reimbursement process was essential. It was possible that the product would be reimbursed by various third-party payers, such as insurance companies, health maintenance organizations, government payers (i.e. Medicare and Medicaid), and each of the payer's reimbursement decisions would be independent. Thus, Genomic Health would have to individually convince payers that the product was medically necessary, appropriate for the specific patient, cost-effective, supported by peer-reviewed publications, and not experimental or investigational. The company also had to decide whether it would manage the reimbursement process on behalf of the patients by filing claims and managing appeals so that doctors would not be billed for the services, and if so, whether they would require patients to sign an Advanced Beneficiary Notice (ABN) so that the patient could be billed if reimbursement was declined. Managing the reimbursement process would increase adoption of the product, but it would also lengthen the company's account receivable cycle. Requiring patients to sign an ABN for an expensive test, on

[43] Zenios, Chess, & Denend, 2006.

the other hand, could slow adoption, and not requiring the ABN would mean that the company would not receive payment for their services unless they were reimbursed. Even when there is an ABN, collecting from patients may not always be possible.[44]

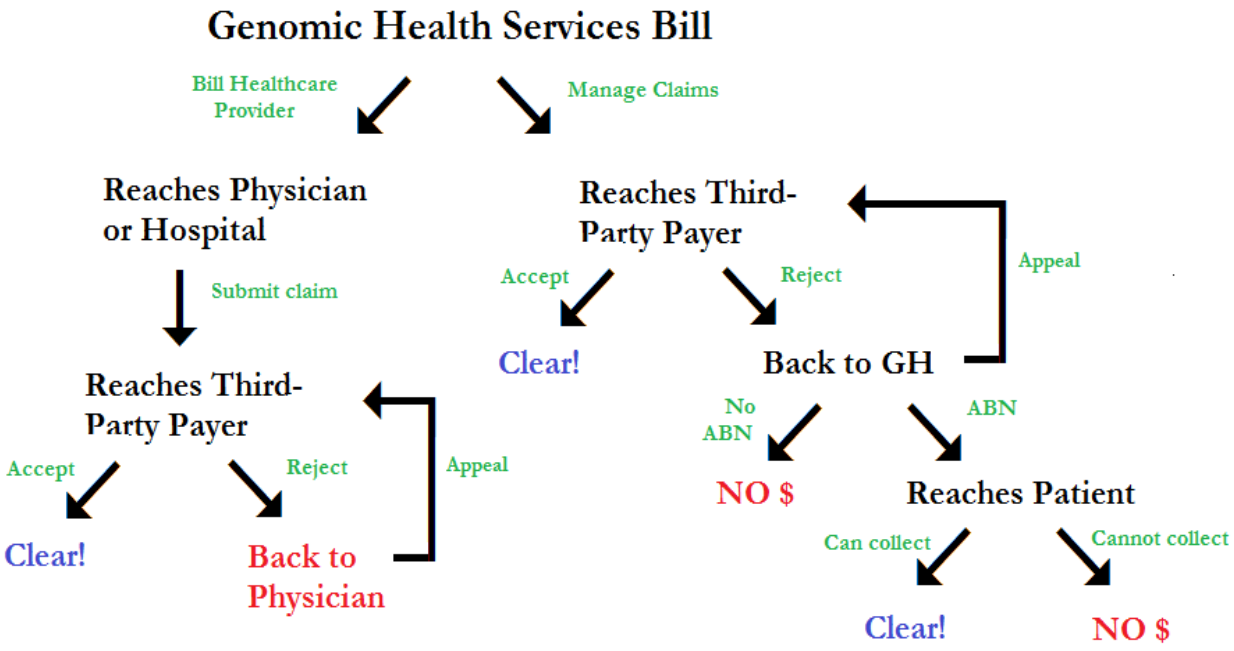

Figure 5: Genomic Health Billing Scheme

With these balances in mind, Genomic Health would have to be prepared to take an economic risk and start providing a service to physicians and patients, bill the insurance companies, and assume financial responsibility if reimbursement was rejected and patients do not pay. Once there are multiple publications in peer-reviewed journals and the physician community demonstrates that they support the test with regular use, payers would be economically motivated to reimburse the test because of money saved every time the Oncotype DX™ platform determined chemotherapy (which can cost over $20,000) to be unnecessary. Furthermore, payers would be reaffirmed that women treated with and without chemotherapy

[44] Zenios, Chess, & Denend, 2006.

were receiving appropriate treatment. Finally, the company would have to assign CPT codes to describe the type of medical procedure performed by the health provider, which would later be reimbursed. The company could stack up multiple codes that applied to their test and request reimbursement for the cumulative amount (which was substantially less than what the company perceived the product's value to be), or they could use a miscellaneous code which would require a manual review and individual defense of every claim.[45]

Ultimately, in their attempts to bring genomics into clinical use, Genomic Health had to navigate a complex system of payment and make some gambles in order to allow useful information to inform medical practice. The company went public in September of 2005, selling over five million shares at $12 a share. Since, Genomic Health's stock prices have peaked at $35 per share in 2012.[46]

[45] Zenios, Chess, & Denend, 2006.

[46] investor.genomichealth.com

23ANDME

In April 2006, Linda Avey and Anne Wojcicki founded 23andMe, with the mission of being the "world's trusted source of personal genetic information." In September 2007, 23andMe had launched their first product to the public: send them $1000 and your saliva, and they would "decode" your DNA.[47] By 2012, as a result of decreases in genotyping costs, the price of 23andMe's product has dropped to $99 (the up-front cost of the product), plus $9 per month for their subscription service.

The Product

23andMe's product provides a holistic interpretation of a person's SNP's. The technology includes a 1.1 million SNP chip, a variation of Illumina's OmniHuman Express chip with an additional 300,000 SNP's based on data from the OMIM database, PharmGKB, and HapMap databases. Because 23andMe chooses a selection of SNP's rather than all 10 million SNP's, the company is essentially placing bets on which SNP's will be shown to have an impact in the future. In addition to predispositions for complex and simple disease like diabetes or Alzheimer's, the product provides insights into ancestry and even fun facts like what genetics can tell a consumer about their hair curl or eye color or even a taste for brussels sprouts. Consumer reactions have varied from valuing the information and seeing the impact on their health decisions to simply enjoying the novelty of peering into their DNA.

[47] Goetz, 2007.

The DTC Model

The basis of 23andMe's business model is the company's articulated core values, which also dictate the way they confront regulatory challenges. The founders have articulated their company's core values as belief in individuals' access to their genetic information, belief in individuals' control over genetic information, and giving people the opportunity to contribute to the advancement of science.[48] As a result, the natural business model that followed was a direct-to-consumer approach: giving patients access and control over their genetic data because they own it, rather than requiring a doctor's prescription like most other genetic tests. In addition to charging for the up-front cost of the product, 23andMe also offers a subscription service, which gives updated reports based on new research findings. There is not a huge difference in the operating cost for one subscriber as opposed to many subscribers, but there is a linear increase in revenue for each subscriber.

While the choice of a business model was motivated by company values, the decision was also a strategic choice. Many companies have attempted to introduce genetics into the clinic by marketing products to physicians. However, 23andMe has cited research stating that it typically takes 17 years for physicians to adopt new technology. Direct-to-consumer marketing can advance the adoption of genomics, as consumers are typically much quicker to react to new technology than physicians or the healthcare industry. By skipping the middleman and putting information directly into the hands of the consumer, consumers are empowered to engage with the service in a way that is not otherwise possible by offering services through doctors and hospitals. Furthermore, the genetic testing service, by providing information rather than

[48] 23andMe.com

medical advice, can help start a dialogue with physicians about the role of genetics in their health.[49]

While 23andMe has generally not marketed their service to physicians on a broad scale, they have sponsored academic programs where medical students can get a steep discount as part of learning about personal genomics integration in medicine for their coursework. The idea is to start with younger generations of doctors, who are more willing to adopt new technology as they are still learning and have not yet become entrenched in certain habits of medical practice. 23andMe hopes to be a disruptive technology, much in the same way WebMD is. Physicians were initially hesitant about their patients trusting internet sources of medical information, like WebMD. However, today, many physicians actually recommend that their patients go online and use WebMD as a resource to learn more and understand what they have discussed with their doctors. In the same way, doctors may eventually recommend 23andMe's services to their patients, especially as a single test would be better to have on file than waiting to administer multiple genetic tests, one at a time, until they are applicable. The general shift in medicine towards prevention could potentially even move things toward partial coverage of 23andMe's services, though this is not a company priority at this point. The company notes that many people are starting to pay for their own healthcare because they know insurance companies are not looking out for their best interests, as the system is not yet based on prevention.[50]

While the direct-to-consumer model has some advantages, it also has limitations. For example, the company does not have the capacity to change the attitudes of physicians or change the standard of care. If enough patients use 23andMe and have conversations with their

[49] Nelson, 2012.

[50] Nelson, 2012.

doctors about the role of genomics, physicians' knowledge and use may be accelerated indirectly. Also, many critics of DTC genetic testing claim that many consumers may not be fully informed when they give their consent and that genetic information can be dangerous in the hands of consumers who don't truly understand it. For example, a 23andMe customer with a family history of diabetes could see a decreased predisposition to diabetes in their genetic profile and decide that they can be a little careless about that aspect of their health when in fact, at this stage, family history is a better predictor of health than genetics. To alleviate dangers of consumers trusting genetic markers over family history, 23andMe has introduced a collaborative family history feature which helps integrate family history into prediction and has a social aspect to it.[51] Furthermore, 23andMe has stressed genetics education and outreach so that people can better understand the information and the risk assessments they are receiving: for DNA Day (April 20) 2012, 23andMe teamed up with KhanAcademy, "the world's online classroom" to create a "Genetics 101" and "Human Prehistory 101" educational video series, publicly available via Internet.[52]

23andMe as a Research Company

In addition to the direct-to-consumer aspect of their business model, 23andMe announced a research arm, entitled 23andWe, in May 2008. By forming research partnerships, the company is able to remain true to their value of giving people the opportunity to contribute to human understanding of genetics. As part of the research initiative, the company provides kits to clinical trials participants or sells consumers' anonymized aggregated data (with

[51] Nelson, 2012.

[52] 23andMe, 2012.

permission). The company also encourages their consumers to fill out surveys regarding phenotypic data to really enrich the quality of research. By May 2011, Wojcicki had gone so far as to say, "We still give people access to their genetic information. But a lot more than that, we are really a research company."[53] In fact, some have asked whether 23andMe should be paying customers for the data, rather than the other way around.[54]

Facing Regulation

Finally, a precarious aspect of the company's history and future includes uncertainties of regulation in the personal genomics industry. Following a government report from SACGHS criticizing lack of regulation of genetic testing companies, public health officials in New York and California sent "cease and desist" letters to genetic testing companies, including 23andMe, claiming that the companies were operating without necessary state licenses. In June 2010, the FDA also contacted 23andMe, stating that they were operating without appropriate FDA premarket review and approval.[55] Because regulation of DTC genetic testing was unprecedented, 23andMe began to work directly with the FDA to navigate the process and discuss standards for the company in context of the industry. Many other companies that had been contacted during this time made the switch from DTC to offering their products through physicians. However, as 23andMe viewed the DTC aspect as an inherent part of their core values, they chose to work with FDA officials and deal with the uncertainty rather than change their business model. 23andMe views FDA involvement as generally positive because consumers

[53] Timmerman, 2011.

[54] Jain, 2012.

[55] Vorhaus, 2010.

and physicians trust the FDA, which means they will trust the product and the company. FDA involvement also helps establish standards and quality control of processes within the company. The downside to FDA involvement is that making changes to the product becomes bureaucratic.[56]

Though privately-owned 23andMe has not released financial data and has not forecasted how the company will be doing, they have noted an accelerated demand presumably due to drops in prices. Also, the company has undergone three rounds of financing, raising money from investors such as Google Ventures, Genentech, Johnson & Johnson, and MPM Capital.[57]

[56] Nelson, 2012.

[57] 23andMe.com

NAVIGENICS

In 2006, oncologist David Agus and human geneticist Dietrich Stephan founded Navigenics, with the mission of "improving health outcomes across the population by providing clinically actionable, personalized genetic insights to motivate behavior change." With an understanding of their genetic predispositions towards certain diseases, Navigenics consumers would make informed health, nutrition, and lifestyle choices. The company officially launched in November 2007, and their flagship service, the Health Compass, was launched in April 2008 at the price of $2500- a cost more than twice as high as its DTC competitors at the time.[58] Navigenics has changed its distribution channel from its original DTC approach, and its prices have lowered substantially since its initial launch.

The Product

Since its inception, Navigenics has maintained a focus on medically relevant information for clinically actionable disease (such as various cancers, heart attacks, diabetes, aneurysm as well as genetic response to medications like warfarin). Because of this focus, Navigenics' Health Compass currently provides risk assessment for 29 health conditions, as compared with 23andMe's assessment of 120 conditions as well as ancestry analysis. Furthermore, the company decided not to provide results for conditions that were not preventable, avoidable, or treatable like Parkinson's or Lou Gehrig's Disease. Navigenics also offered all customers, even in the early stages, access to genetic counselors to discuss results, identify resources, and facilitate a dialogue with their healthcare provider. The Health Compass would then enable physicians to develop a

[58] Chess & Rosenthall, 2011..

more personalized, focused, and prevention-based health plan. The team felt that the scientific rigor of Health Compass combined with the built-in counseling service merited a premium price.[59]

A New Business Model

Given the media hype surrounding genomics and its potential for personalized medicine, Navigenics anticipated immediate demand, but customer uptake fell short of these expectations. After several months of slow adoption, the company solicited feedback, which revealed that consumers found the product too expensive and that the clinical nature of Navigenics' offering meant that physicians needed to be involved in the process. The team initially considered a strategy where customers pushed the Health Compass to their doctors, similar to the Cord Blood Registry approach, but Navigenics did not have the resources or infrastructure to support the marketing effort required for that strategy.[60]

By fall of 2008, the company began evaluating a shift from DTC to a "facilitated model," in which doctors would initially facilitate distribution of the service to the user. By this new model, Health Compass could be accessed through a physician recommendation to their patient or through a patient request for access to the test from their physician (if the doctor was in the Navigenics Network). Thus, the service would be incorporated into an overall prevention and wellness strategy or would confirm risk factors for diseases already identified via family history

[59] Chess & Rosenthall, 2011..

[60] Chess & Rosenthall, 2011.

or health parameters. Furthermore, the model would leverage the information exchange between patients and doctors, while making the physician networks a more accessible user base.

However, to utilize the facilitated model, Navigenics would have to invest in preparing the physician community to incorporate genomics into their practice. Many doctors reported interest but insecurity over lack of genetics integration and education in medical school, while others would need to be convinced that the Health Compass was worth more than existing diagnostic tests already being used in the clinic. [61] Accordingly, Navigenics would have to invest in education and demonstration of high clinical standards.

Strategic Partnerships

Because of lack of reimbursement, Navigenics first targeted "concierge doctors," who accepted an annual fee, rather than insurance, for unlimited care. By December 2008, the company had partnered with MDVIP, a large concierge physician network, to launch a pilot program. As part of the program, physicians and patients would be educated about genetic testing, tests would be marketed to the patients, and physicians would distribute the tests to their patients. They soon partnered with Medcan Clinic and a concierge clinic called The Village Doctor. Throughout 2009, the company developed a physician portal so that participating physicians could enroll in continuing education classes in genomics and access their patients' results.[62]

[61] Chess & Rosenthall, 2011..

[62] Chess & Rosenthall, 2011..

Navigenics also looked for partnerships beyond concierge physician networks to facilitate large scale product delivery. The company looked to large employers, as they were responsible for 22 percent of the $2.2 billion in healthcare spending in 2008 according to CMS.[63] With healthcare costs rising, employers were increasingly investing in prevention and wellness program to encourage more active and healthier lifestyles amongst employees. Furthermore, Navigenics CEO, Dr. Vanier, claims, "In 40 to 50 percent of the cases, they [employers] pay for drugs that don't work on people due to their individual genetic variation or because people don't take the drugs in the first place because of lack of medical compliance. The value proposition we bring to them is saying there is data emerging which indicates that when you show people their genetic predisposition, they become more medically compliant and motivated to engage in a healthier lifestyle."[64]

The company spent over a year of trying to sell into corporate benefits groups, which was difficult due to the complex benefits enrollment process and the unfamiliarity of the product. In early 2009, Navigenics established their first corporate partnership with Cisco Systems. The program was piloted as part of Cisco's wellness-based incentive package: the first of a select number of top Cisco executives to schedule a physical would receive a free genetic test. Participation was immediate, and Cisco's management decided to expand access to their larger employee base. Though the services were not free, the prospect of access to cutting-edge technology compelled many employees to sign up and gave employers some cache. As Silicon Valley appeared to be a great cultural fit, Navigenics targeted other like-minded high tech

[63] CMS, 2010.

[64] Chess & Rosenthall, 2011.

employers such as Life Technologies and Intel.[65] In April 2011, Navigenics moved beyond just individual companies by announcing a partnership with Highmark Blue Shield, a large insurance provider, to integrate the Health Compass into their employer wellness programs. As such, Navigenics could potentially reach millions of patients whose employers are under Highmark's plan.[66]

In addition to seeking partnerships to distribute their product, Navigenics sought out partnerships to increase adoption and to expand their client base. They developed continuing education programs for physicians with both the American College of Preventative Medicine and Medscape. They launched research studies with the Scripps Genomic Health Initiative (SGHI) to evaluate consumer attitudes towards genetic testing and with Mayo Clinic to understand how physicians and patients use genetic information. Navigenics also partnered with educational institutions to offer students access to their genetic tests through the Beth Israel Deaconess Medical Center's Personalized Genomics and Next Generation Sequencing Training Program and Stanford's Genomics and Personalized Medicine course for medical students.[67]

Regulatory Challenges

The CDC published standards for identification of correlation between genetic markers and specific medical conditions. Navigenics' selection criteria met or exceeded the CDC's standards, given the exclusively clinical nature of their services. Other genetic companies set

[65] Chess & Rosenthall, 2011.

[66] Ray, 2011.

[67] Navigenics.com

their own thresholds as well, leading to variability, rather than an absolute bar, for what constituted quality data.[68] In 2009, an article in *Nature* criticized the inconsistencies between 23andMe and Navigenics. Furthermore, in light of public skepticism and industry growth, the Government Accountability Office (GAO) conducted a second investigation and released a report entitled "Direct-to-Consumer Genetic Tests: Misleading Test Results Are Further Complicated by Deceptive Marketing and Other Questionable Practices." All four companies profiled in the report (Navigenics, 23andMe, deCODEme, and Pathway) had to appear at the Congressional hearings in July 2010 and answer to the accusations from the GAO report in order to assure the government and public of company integrity and product quality.[69]

The sudden onset of criticism combined with the lack of previous regulation, which had encouraged the entry of many low-quality players in this space, had resulted in possibly irreparable damage to the integrity of the genomics industry. Furthermore, the future of regulation was uncertain and unstable. The Navigenics team believed the regulatory challenges had already affected their business: a potential partner company chose to put a deal on hold after the second GAO report was released.[70] Finally, the resulting public skepticism may jeopardize the existing customer base.

Navigenics remains privately owned and has not released financial data. However, the company has raised over $40 million dollars over the course of three rounds of financing.[71] Top

[68] Ng, 2009.

[69] Vorhaus, 2010.

[70] Chess & Rosenthall, 2011.

[71] Chess & Rosenthall, 2011.

venture capital firms such as Kleiner Perkins Caufield & Byers, Mohr Davidow Ventures, Sequoia Capital, Proctor & Gamble have all invested in Navigenics.[72]

[72] Navigenics.om

POLICY ANALYSIS

History of the Genomics and Personalized Medicine Act

With the underlying vision, of medical practice which routinely uses genomics to enable predictive and preventative medicine, permeating media commentary, the public has turned to policymakers to put in place the regulatory and financial systems in place to support personalized medicine.[73] In 2006[74] and 2007[75], then-Senator Barack Obama introduced the Genomics and Personalized Medicine Act, but in both cases it died after being referred to different Committees. In 2008[76] and 2010[77], Representative Robert Kennedy re-introduced the Genomics and Personalized Medicine Act, but again it died in both cases. The discussion will focus on the most recent version of this bill: the Genomics and Personalized Medicine Act of 2010, or H.R. 5440 (111th). The bill has a stated aim of securing "the promise of personalized medicine for all Americans by expanding and accelerating genomics research and initiatives to improve the accuracy of disease diagnosis, increase the safety of drugs, and identify novel treatments, and for other purposes."[78]

In addition to Rep. Patrick Kennedy's [D, RI-1] sponsorship, the bill had six co-sponsors in 2010: Rep. Robert Andrews [D, NJ-1], Rep. Michael Capuano [D, MA-8], Rep. Anna Eshoo [D, CA-14], Rep. Alcee Hastings [D, FL-23], Rep. Tim Holden [D, PA-17], and Rep. Jared Polis

[73] Personalized Medicine Coalition, 2012.

[74] S. 3822 (109th), 2006.

[75] S. 976 (110th), 2007.

[76] H.R. 6498 (110th), 2008.

[77] H.R. 5440 (110th), 2010.

[78] H.R. 5440 (110th), 2010.

[D, CO-2]. The bill also had the support of the Personalized Medicine Coalition, whose members include "a broad spectrum of over 200 academic, industry, patient, provider, and payer communities" that "seek to advance understanding and adoption of personalized medicine concepts and products for the benefits of patients."[79] On the other hand, the College of American Pathologists voiced concerns about some specifics of the bill.[80] After being introduced to Congress and referred to the House Committee on Energy and Commerce, GPMA 2010 died. In order to assess the role of legislation in translating genomics research into clinical use, the efficacy of this bill and how it affects stakeholders will be evaluated, and the bill's evolution since 2006 and potential changes for a future iteration will be considered.

Bill Overview

GPMA aims to bring personalized medicine to all Americans in the form of increased genomics research, use in clinical settings, and establishment of some regulation for personalized medicine products. The complexity of this goal requires many different initiatives. First, GPMA establishes the Office of Personalized Healthcare (OPH), a centralized agency that coordinates efforts in the public and private sectors regarding standards of safety, efficacy, and clinical validity and utility for personalized medicine. GPMA would also increase and accelerate research in genomics and personalized medicine. It would establish a national biobank in order to collect genomic data and associated clinical information for research purposes, as well as grants to develop and expand the biobank. The Act also aims to improve genetics and genomics training

[79] www.personalizedmedicinecoalition.org

[80] College of American Pathologists, 2010

for diagnosis, treatment, and counseling. Taking into account all stakeholders, GPMA would institute a study by the Institute of Medicine to determine a more effective billing, coverage, and reimbursement model to be recommended to Congress at a later date. It would also encourage companion diagnostic testing for new drugs in order to reduce risk and incidence of adverse drug reactions. GPMA would expand efforts to educate and increase public awareness about genomics and personalized medicine and its applications. Finally, to implement these measures, it authorizes appropriations of a total of $66 million for 2011, with similar sums as necessary from 2012 to 2016.[81]

Office of Personalized Health

GPMA establishes an Office of Personalized Health (OPH) within the Department of Health and Human Services (HHS). Its role is to oversee implementation of GPMA initiatives and to coordinate cross-agency activities related to genomics and personalized medicine to ensure that personalized medicine meets the highest standards of safety, efficacy, and clinical validity and utility.

The OPH is a new addition to previous versions of the bill that had instead established the Interagency Working Group (IWG), which was mainly responsible for reviewing and prioritizing initiatives, developing guidelines, and making recommendations. By contrast, the OPH has a much more active responsibility of developing a strategic, long-term plan as well as identifying, prioritizing, and addressing challenges. The intention is that OPH would serve as

[81] H.R. 5440 (110th), 2010.

more of a "centralized taskforce to direct the implementation of GPMA initiatives" rather than another committee resulting in redundancy and inconsistency. If the OPH's roles and responsibilities remain clearly separate from those of other agencies like the FDA, the CMS, or the CDC, the OPH could be effective rather than fettered by bureaucracy.[82] Though GPMA mentions collaboration across government organizations, it does not address specifics of the role and authority of each agency in relation to each other. Therefore, the proper execution of creating this office is essential to the success of the bill's initiatives.

Role of FDA

GPMA includes a few sections on the FDA's role in personalized medicine, with provisions to permit the agency to require that sponsors of a drug develop companion diagnostic tests to address safety concerns. The FDA is also responsible for clarifying and issuing guidance on the labeling of personalized medicine products, regulating automated clinical decision support systems, collecting genetic information (rather than race/ethnicity) to predict drug response, addressing concerns of adverse events resulting from use of personalized medicine products, and terminating misleading or false advertising campaigns about the benefits or risks of personalized medicine products.[83]

The permission given to the FDA to require the development of companion diagnostic tests is a departure from the 2007 and 2008 versions of the bill, which merely allowed the FDA

[82] Bushee, 2010.

[83] H.R. 5440 (110th), 2010.

to recommend development. This provision is a reflection that GPMA looks favorably upon pharmacogenomics as sometimes necessary to therapeutic treatment, and this allows the FDA to impose even more obstacles to the drug development and approval process. It also may reflect a growing trend of reliance on genomic data to make decisions about selecting and administering therapeutics.[84]

GPMA's mention of misleading advertising campaigns about all personalized medicine products, rather than previous versions' focus solely on advertising of genetic and genomic tests, is also notable.[85] This provision is important, especially due to the current prevalence of direct-to-consumer (DTC) genetic testing and the uncertainty of regulation over DTC tests. For example, despite any previous guidelines regarding genetic tests, the FDA and FTC issued cease-and-desist letters to many DTC companies in 2010. Furthermore, the GAO report highlighted "misleading test results" and "deceptive marketing practices" of DTC companies and was forwarded to the FTC and FDA, who have begun taking action.[86] While FDA and FTC regulatory oversight is essential to protecting the public (as a consumer or as a patient), the bill can provide some consistency and guidelines so that industry knows what to expect before being chastised.

[84] Bushee, 2010.

[85] Bushee, 2010.

[86] Bushee, 2010.

Institute of Medicine Study: Financial System

In order to address the lack of financial infrastructure in place to accommodate genomics and personalized medicine, GPMA calls for a study by OPH and the Institute of Medicine to review the current billing, coverage, and reimbursement for personalized medicine products and services. The study is to include recommendations of insurance models, tax credits, and incentives to promote R&D to advance personalized medicine. Furthermore, the study will be conducted with the consultation of all stakeholders: consumers, healthcare providers, scientists and researchers, private payers, representatives from clinical and academic labs, and representatives from biotech, pharma, and diagnostics industries.[87]

As many genetic and genomic tests are not yet covered by insurance, the study seeks to address the disincentive of disproportionate costs that may keep some companies from entering the market. While this bill does not actually create the financial infrastructure, all stakeholders' perspectives are accounted for in the committee which makes a recommendation to Congress for the eventual introduction of further legislation. Also, by only calling for a recommendation to Congress rather than including specific financial legislation in this bill, GPMA is made less controversial (but also less tangible) and allows Congress to make gradual progress in addressing this issue rather than being overly ambitious. Further legislation may include tax credits for companies entering this market, Medicare coverage of personalized medicine, or patent expansion on or market exclusivities to help incentivize developers to pursue personalized

[87] H.R. 5440 (110th), 2010.

medicine product development (which could be especially important as patent protection for personalized medicine technologies are under review in the courts).[88]

Public Awareness and Education

GPMA also includes a section on the CDC's role in personalized medicine, with provisions to increase public education and awareness of the application of genomics and personalized medicine to health and disease. It also calls for the CDC to conduct analysis, in conjunction with the FDA and FTC, on the impact of DTC testing on public health and possible interventions to protect the public from potential harms of DTC.

The public awareness provision specifically calls for the development and dissemination of informational resources on the utility of personalized medicine products. This may further the goal of allowing the public to understand the options available to them and promoting the use of helpful products which would otherwise be overlooked. It recognizes the patients as important stakeholders in personalized medicine and gives them resources to learn more about this technological development as it pertains to their health. Furthermore, the provision requires "the ongoing collection of data on the awareness, knowledge, and use of genetic and genomic tests through public health surveillance systems, and analysis of the impact of such tests on population health."[89] This data could prove invaluable in understanding the importance of genomics and personalized medicine in practice, and it could act as a measure of the success of GPMA and the OPH. The impact on population health relates directly to GPMA's stated

[88] Konski, 2011.
[89] H.R. 5440 (110th), 2010.

aim of securing "the promise of personalized medicine for all Americans." It may also be helpful to set specific goals for numbers in order to compare expectations with the data and make recommendations accordingly. Finally, the CDC is responsible for the integration of validated genetic/genomic tests in public health programs and the evaluation of lab standards and practices in order to ensure quality laboratory services.

All of these provisions reflect a commitment to ensuring that the benefits of genomics and personalized medicine are applied to public health.

Cost of Investment

In total, GPMA authorizes the appropriation of $256 million of spending for the first year, with similar sums as necessary for the next four years, which adds up to a $1.28 billion investment over the course of five years. It is worth noting that GPMA authorizes the appropriation of this money, rather than actually appropriating it, so the final cost may be lower than what is stated in the bill.

In addition to an investment in the potential benefits in public health and medical practice, the spending in these bills is often seen as a financial investment. For comparison, according to the Batelle Report on the economic impact of the Human Genome Project, the federal government invested $3.8 billion in the HGP through its completion in 2003, and by 2010, the total investment had reached $5.6 billion. However, the project, associated research, and industry activity directly and indirectly generated a total of $796 billion in U.S. economic output, including $244 billion in personal income for Americans and 3.8 million job-years of

employment. This shows a return on investment of 141 to 1, and the government revenue from 2010 "nearly equaled the entire 13-year investment in the HGP."[90]

Finally, while GPMA poses many new potential costs, effective preventative medicine would reduce costs in treating diseases which have progressed much further.

Concluding Analysis of GPMA

GPMA has evolved immensely since its first introduction in 2006, from the establishment of the Office of Personalized Healthcare rather than the Interagency Working Group, to mandating a study of financial support by the Institute of Medicine instead of specific tax credits and financial solutions. As a whole, GPMA is now broader and encompasses more aspects of policy on Personalized Medicine. It addresses the strategic and long term vision through the creation of the Office for Personalized Healthcare, integrates the roles of other government organizations which have overlapping goals such as the National Institutes of Health, the Food and Drug Administration, and the Center for Disease Control, addresses public health impact, aims to understand financial incentives to support the technology, regulates the technology, and establishes a biobank and associated research projects.

The bill also provides a framework through which future recommendations on policy can be made. This is at once an advantage and disadvantage: while a committee, inclusive of all stakeholders, will have the time and expertise to make an appropriate recommendation, there are no guarantees that further, specific legislation will pass. As a result, it may be easier to rally

[90] Battelle Technology Partnership Practice, 2011.

support for the bill, but it is also more likely that less action will be effected. If too much is left ambiguous, GPMA would lack transparency and accountability. Instead, it may be advisable for the Institute of Medicine to convene a committee to recommend a financial support system in the near future rather than wait for this legislation to pass. Then, that recommendation can be incorporated into a future iteration of the bill, resulting in specific, well-informed action that is fair to the stakeholders. Additionally, though it is wise to have a centralized and strategic taskforce be responsible for following through on the initiatives of GPMA, delineating authority of overlapping groups is key to preventing unnecessary bureaucracy. Also, GPMA, like GINA, does not address informed consent, consumers' genetic privacy rights, or intellectual property issues, such as ownership, patents, and patient access; though, perhaps this is best left to courts to decide.

GPMA calls for the instatement of a national biobank to further research purposes, in spite of patient privacy risks associated even with anonymized data. However, it neglects to address or support another area of research which could potentially have a high impact on personalized medicine: the specific role of healthcare IT devices and services in personalized medicine. For example, IBM intends its artificial intelligence computer system Watson to be used in a clinical context to suggest diagnoses and treatment in support of the doctor. Clinical decision support, if developed and implemented successfully, may contribute immensely to the aims of GPMA. Furthermore, pairing the introduction of clinical decision support using computers with a transition to electronic medical records (EMR), another aspect of healthcare IT services not mentioned in the bill, could make medicine more efficient than ever. It also would allow physicians to tailor their approach to each individual patient's personal medical

history more easily due to the improved organization and display of the medical record.[91] The advent of clinical decision support and EMR could contribute enormously to personalized medicine in the healthcare setting, and therefore warrants some mention in GPMA.

Finally, is passing GPMA even feasible? With Congress deadlocked over many issues, especially in regards to the budget and spending, it seems unlikely at present that GPMA will pass as is. Given the huge resistance to the universal healthcare bill in 2010, GPMA is likely to be seen as unnecessary and even overly indulgent. This point would be furthered by academic research stating that genomics and bioinformatics research has been markedly over-optimistic.[92] The field is certainly fascinating from a scientific perspective, but many critics will rush to make judgments that it is not useful in a clinical context. Again, addressing these arguments before introducing GPMA in the future could make the bill much more feasible, especially if the economic and political climate has improved.

GPMA has changed substantially over the years, and the bill in its 2010 form includes some important topics to legislate: DTC regulation, public awareness, genomics training, study for a financial model, etc. In spite of its positive qualities, a few more changes are necessary to guarantee that this bill will be effective and fair to all stakeholders. Critics have been skeptical of Congressional inactivity, but in this case, reasons for its death the past four times could be legitimate. GPMA would be considerably improved by inclusion of a few more specifics, as it would ensure more immediate action. The bill, as it stands, has pushed an important technology into the sphere of legislation and given policymakers something to build off of. If we are to truly realize the potential of genomics and personalized medicine, we must continue to

[91] Fernald, Capriotti, Daneshjou, Karczewski, & Altman, 2011.
[92] Jelizarow, Guillemot, Tenenhaus, Strimmer, &Boulesteix, 2010.

work with this document and the stakeholders involved in order to pass supportive and enabling legislation.

DISCUSSION AND CONCLUSION

Commercial Business Models in Genomics

Each of the companies discussed in this thesis use very different business models in their goals to promote widespread use of genomics. 23andMe maintained their DTC approach, as part of a values statement as well as acting on the idea that consumers would be quicker to adopt new technologies than physicians. Meanwhile, Navigenics made the switch to offering services through physicians and clinics, believing it to be more effective than their initial DTC approach which necessitates an "end-run" around doctors. Finally, Genomic Health developed tests specifically for the purpose of informing medical decisions of appropriate cancer therapy treatment and thus made clinical validation and potential reimbursement an essential part of their business model.

Some companies may begin to integrate these various approaches. For example, Personalis, a new startup planning to offer personal whole genome interpretation with scientific rigor, is currently focusing on product development rather than commercialization.[93] We may see Personalis incorporate the significance of clinical validity, which is at the core of Genomic Health's business model, combined with the larger scope of the entire genome and its implications for the average person which Navigenics and 23andMe value.

[93] Siegel 2012.

Competitive or Synergistic?

While many companies within the genomics industry may be seen as competitors, the different approaches can also be viewed as serving different spheres and different purposes. 23andMe is bringing genomics into the public spotlight, encouraging genetics education, and teaching people to understand the significance of genetics in their health. Essential to this is spreading the knowledge that genetics is not deterministic and that behavior can have a much more powerful influence on health. 23andMe truly seeks to contribute to a cultural shift within society, empowering patients with respect to their health. This goal, rather than competing, is synergistic with the goals of many other genomics companies that seek to bring genetics directly into the clinic. Patients who are aware of and understand genetics will be more able to understand their medical treatments, especially when physicians' medical decisions are informed by the patient's genetics or a patient's symptoms reflect their genetics. Many critics have called 23andMe's services "recreational" or a "novelty." Indeed, this could be very true for many consumers without any surprising biomarkers. However, this service can set the stage for a future where more concrete and actionable genetic discoveries are being made. After all, if a "genomics revolution" is taking place, should it not include awareness and understanding of the general public whose health is at stake?

On the other hand, Navigenics chose physician networks and partnerships as their primary distribution channel. People often cite the slow adoption of electronic vs. paper medical records as a prime example of physicians being resistant to incorporating new technology in the clinic. By marketing directly to one source of resistance, encouraging use by physicians, and incorporating their feedback, Navigenics is better equipped to start a movement within the

physician community than a company out of touch with physician concerns. Also, Navigenics has a stronger focus on health and automatically engages both the patient and physician (and even genetic counselors) in conversation over their personal results. Finally, when people trust their healthcare providers, they are more likely to take genetics seriously—and in the event that they take it more seriously than is appropriate given the information, genetic counselors are accessible to educate and help the patient. Because the cultural shifts are targeted at different segments of the population, that is the physician community vs. the general public, the business models of Navigenics and 23andMe actually do result in a somewhat surprising synergy.

Finally, Genomic Health is a fascinating case of how a corporation can make genetics and genomics clinically relevant and can tangibly improve and inform clinical decision-making. While assessment of genetic risk can often seem ambiguous, Genomic Health gives actionable information and supports it with clinical validation and a pharma approach, so that reimbursement is feasible. This is an especially viable approach with cancer genomics at this point. Though it may not be appropriate for holistic genome interpretation services yet, the approach is likely adaptable for companies that have some sort of focus or specialization, especially because genetic diagnostic tests have precedent in clinical decision-making and the reimbursement process. If clinically significant findings from genomic data become even more common, more holistic services may look to emulate the example Genomic Health has set in choosing a business model that incorporates the difficult reimbursement process.

Of course to chalk up the different approaches of genomics companies to a purely synergistic effect would be misguided and even naïve. Some of these companies have comparable business models, and even those that do not will eventually, and to some extent

have already, come into conflict in capturing the market. The business model that is most successful in the long-term will likely be determined by how people continue to view genomics. Will the public see it as analogous to monitoring cholesterol or blood pressure, or will it be viewed as a medical test like an MRI, X-ray, or CT scan? And how the public views genomics will undoubtedly be influenced by media coverage, educational outreach done by companies like 23andMe, and the amount and significance of clinically relevant knowledge gained from the masses of data being collected. In short, this is not an easy prediction to make. Furthermore, the fact that Genomic Health is the only company of the three to have gone public is perhaps demonstrative of the idea that at this time, genomics is viewed as useful in a very specific clinical context, rather than in the broader world of the consumer or patient.

Reimbursement

All three companies examined have chosen different paths to facing the reimbursement process. As 23andMe does not give medical advice, at this time, the service does not qualify for reimbursement. This is likely to remain the case, at least unless 23andMe makes reimbursement a priority and adjusts their business model accordingly. Meanwhile, Navigenics offers reimbursement for patients who are enrolled in Flexible Spending Accounts (FSA's) and Health Savings Accounts (HSA's) through their employers. Finally, Genomic Health has the most complex and careful plan for reimbursement of the three, detailed in the case research, in which the company committed significant R&D to clinically validate their findings as well as demonstrate cost-effectiveness of the test. One trend noted from these cases is that the onus of obtaining reimbursement for patients and physicians seems to fall on the company providing the

service. It is possible that with many companies (especially in molecular diagnostics) following similar paths to reimbursement as Genomic Health, CMS and other insurance providers will come to expect claims for genomics products and accelerate the process, especially if the system is regulated effectively.

While many have criticized lack of reimbursement, this barrier may actually be somewhat useful in ensuring that widely adopted genomic products are rigorously proven to be effective and useful. Without this challenge, medical costs may rise, at times without the corresponding health benefits. Furthermore, this obstacle ensures that the genomics industry will preserve its integrity. Of course, there must be some balance because imposing obstacles which are too difficult will compromise the life of the industry as a whole. In this case, legislative measures to instate financial incentives, such as tax credits and patent exclusivity, would allow more companies to have an opportunity to prove the validity and efficacy of their genomic products. Also, if CMS and industry collaborate to open up communication during the product development phase, insurance companies may be better equipped to keep up with the pace of introductions of new genomic products and evaluate them more efficiently.

Regulation

The uncertainty associated with the current state of FDA regulation on a case-by-case basis, rather than industry-wide guidance, has huge potential effects on the genomics industry, including reduced access to capital, fewer products, fewer entrants, litigation risks, reduced

collaboration, and even overseas development.[94] This aspect of regulation needs to be addressed directly by the FDA or incorporated into legislation, as necessary. While relatively well established companies like 23andMe and Navigenics have been able to incorporate these challenges into their business models, industry and the economy may lose out on valuable opportunities if no changes are made to this process. Though some regulation is necessary, it would be more effective if it were well-understood by prospective and current companies. Combined with the lack of reimbursement, lack of clarity by regulatory bodies can seriously hurt this nascent field.

STS Perspective

This is also a fitting opportunity to apply STS principles to this discussion. First of all, this technology exists within a complex socio-, cultural, environmental system (known as the SCES model), with individual agents (such as scientists and entrepreneurs) pushing the technology forward. Genomics as a technology may have profound consequences on the SCES background. For example, would an overemphasis on the predictive power of genomics create an ideational cultural shift of belief in genetic determinism? Or will perhaps the constant need for genomics to be "actionable" induce an ideational culture of over-optimism? Is it possible that the lack of reimbursement in personal genomics will further dichotomize socio-economic classes in regards to quality of healthcare? Could genomics change the very "fabric of everyday life" as so many technologies have? Widespread integration of genomics opens the doors to all of these questions, questions we must consider carefully as technology and society continue to interact with and shape each other.

[94] Vorhaus, 2011.

The STS lens can also be applied to break down the relationship between technical change and ensuing social change [TCESC relationship]. Using the IDUAR model, the social change resulting from genomics technology can be delineated into innovation, diffusion, user groups, adaptation, and resistance of genomics. Innovations in genomics typically come from novel findings in academia or in R&D divisions of companies in the genomics sphere. Diffusion varies from DTC marketing, physician recommendations, even to participation in clinical studies which have a genomic component. Typically agents of this diffusion must be companies offering incentives like "free" services or perhaps potential health benefits from participation. The user groups include physicians looking to improve medical practices and decisions as well as patients/consumers looking to prevent health problems. To effectively use the technology, users must have a basic understanding of genetics and what their genetic information means in context of their health. Finally, barriers of resistance, the focus of this paper, are largely lack of financial incentive and reimbursement, especially given high costs, as well as uncertainties of regulation of companies in the industry. One could also argue that the limited extent of genomics-based discoveries at this stage of genomics research, which is needed to make wider claims on a person's health, is a barrier of resistance.

Finally, it will be productive to discuss the ethical responsibilities of scientists and engineers with regards to genomics. In this multi-player situation within a medical context, scientists and engineers are first and foremost responsible for helping, or at the very least not hurting, patients. This responsibility plays out in the accuracy of data, protection of privacy, and accurate relay of information. It can even play out in the translation of potentially life-saving academic discoveries so that patients and taxpayers have access to the benefits of research, which they may have in part helped to fund. Most of these responsibilities in previous sections

as well as the role of regulation in ensuring these responsibilities are met have been discussed in previous sections.

Broader Implications

While realizing the full potential of genomics is an incredibly exciting idea, the "personalized medicine" revolution does not begin and end with genomics. With other huge changes in healthcare such as the introduction of electronic medical records, online access to doctors through smartphone apps like HealthTap, and detailed medical explanations online at WebMD, the entire landscape of medicine may be transformed. There are also open science projects like Promethease, which allows users to upload their genome and gain new insights into interpretation of their SNPs for free. What we are beginning to see here is a shift in medicine towards engaging the patients beyond just a doctor's appointment, giving patients unprecedented access of medical information. Computer science may have taken off in the 80's, but computation and the Internet are starting to alter the relationship patients have with their doctors and with their health today—and this is only just the beginning.

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APPENDIX A: Timeline of DTC Regulation

2006: First GAO report on DTC
FDA/FTC/CDC release fact-sheet advising skepticism in genomics
CLIA certification process available since 1988

2007: State Statutes prohibit/restrict DTC
Possible (uncertain) regulation of some laboratory-developed tests (LDT's, include DTC) by FDA; no formal action

2008: SACGHS reports gaps in regulation of genetic testing: insufficient oversight in lab quality, clinical validity, lack of knowledge of nature/use of genetic test; recommends FDA regulatory oversight, creation of mandatory, public registry of lab tests
NY, CA public health officials tell Navigenics, deCODE, & 23andMe "cease and desist"

2009: Congress "secretly" instructs GAO to begin second investigation
Continued interest in FDA regulation of some LDT's; no action
CA legislature considers bill creating special regulatory framework for "post-CLIA bioinformatics services"; does not materialize
Academics and commentators stress self-regulation; no major changes

2010: NIH announces creation of voluntary genetic testing registry
FDA sends letters to 20 genetic testing companies about lack of FDA clearance/approval
FDA announces plan to regulate ALL LDT's
Congress announces its DTC investigation
July: Congressional public hearing on DTC, 2nd GAO report at center

2011: FDA sends 3 more letters
March: FDA holds public 2-day meeting on DTC
May: FDA drafts guidance for research-use only (RUO) and investigational-use only (IUO) in vitro diagnostic products rules for marketing/commercializing

APPENDIX B: Sample Questions for 23andMe Interview

1) As of now, 23andMe primarily offers direct-to-consumer products. Are there any plans to change the monetization scheme or target audience? For example, are there plans for use in a clinical setting?

2) What was the logic in adopting a direct-to-consumer approach?

3) What do you see is the healthcare provider's role in genomics? How is this incorporated into the product/services?

4) How might the cost decreases for whole genome sequencing affect 23andMe's offered services and technology?
    a. Will 23andMe eventually switch to whole genome sequencing?
    b. Increased competition from other companies?
    c. Increased genetic information?
    d. Increased services?
    e. Decreased costs?
    f. Broader changes in approach?

5) How is 23andMe different from other genetic interpretation companies, like Navigenics, Knome, deCODE, Pathway, Counsyl?

6) What are the long-term goals of 23andMe?
    a. In the complex relationships between those researching sequencing technology, those researching genomic interpretation, doctors, and patients, what is the company's role?
    b. Who do you see as your customers in the long run?
    c. How does regulation and legislation fit in with 23andMe's vision of personal genomics?