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Human Genome Testing

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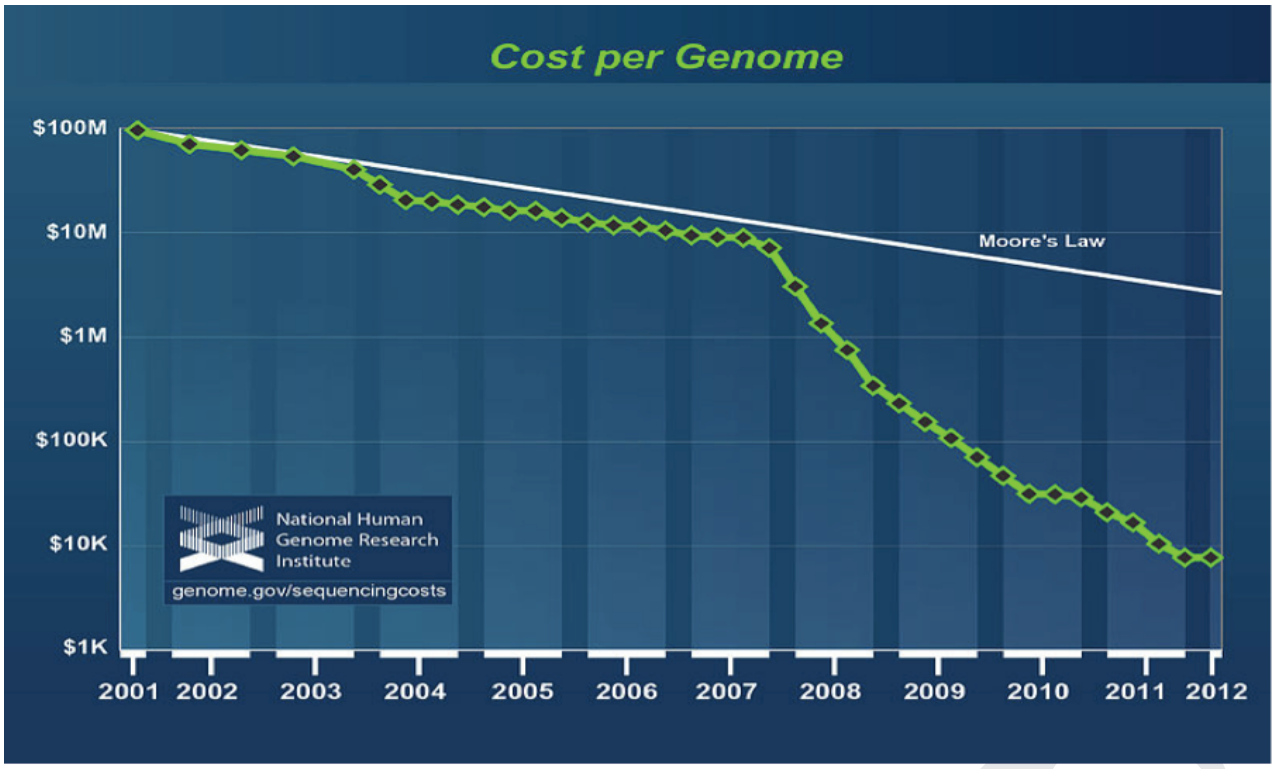
The Coleman Fung Institute for Engineering Leadership, launched in January 2010, prepares engineers and scientists – from students to seasoned professionals – with the multidisciplinary skills to lead enterprises of all scales, in industry, government and the nonprofit sector.

Headquartered in UC Berkeley's College of Engineering and built on the foundation laid by the College's Center for Entrepreneurship & Technology, the Fung Institute combines leadership coursework in technology innovation and management with intensive study in an area of industry specialization. This integrated knowledge cultivates leaders who can make insightful decisions with the confidence that comes from a synthesized understanding of technological, marketplace and operational implications.

Abstract: The price of sequencing whole genomes has been rapidly declining over the last few years. Genetic testing is becoming accessible and affordable to the common public, and start-ups are beginning to provide limited screening services that allow customers to explore their DNA. In this paper, we hypothesize that genome sequencing will revolutionize medical care and impact how drug companies operate and advertise to customers.



1. Existing Landscape

The Human Genome Project, an international scientific research project, was started in 1990 with the goal of determining the sequence of the chemical base pairs that make up the human DNA. A working draft of the genome was announced in 2000 and a complete one in 2003. Most of the government sponsored sequencing was performed in universities and research centers.

The Genographic Project, a project of the National Geographic Society and IBM, was launched in 2005 and aimed to collect DNA samples to map historical human migration patterns. As of December 2012, the project had 500,000 public participants. This effort helped to create the direct-to-consumer (DTC) genetic testing industry.

Today there are several companies engaged in consumer-oriented genome sequencing. The following fourteen companies (Appendix I - Table A) were evaluated for this project: 23andME, deCode Genetics, Navigenics, Pathway Genetics, Lumigenix, i-gene, Genotek, bio-logis, Ancestry DNA, Knome, Counsyl, Family Tree DNA, Personalis and Xcode Life Sciences.

The majority of these companies started between 2006 and 2011 with the exception of deCode genetics and Family Tree DNA, which were founded in 1996 and 1999, respectively. Most are US firms, two are Russian and one each is from Iceland, Germany and India. All companies appear to offer their services exclusively within the country in which they are based.

Most companies perform only partial genome screening and offer their services directly to consumers. Today, Knome is the only company that offers whole genome screening to consumers while 23andMe has the declared goal to do so eventually. Personalis (the only other company currently performing whole genome screening) exclusively works with medical and research institutions.

DTC services are offered in the following areas (Table B):

- *Ancestry* – trace origin
- *Disease* – likely hood / diagnosis of lifestyle (heart, stroke, obesity, various types of cancer, etc.) or rare diseases (cystic fibrosis, sickle cell anemia, etc.)
- *Drug Response* – likely hood to respond to certain drugs with certain level of intensity
- *Carrier Status* - detection of recessive (mutated) genes / risk assessment for family planning

Only two of the companies researched offer the full range of services listed above (e.g. 23andME and i-gene, a Russian copy of 23andME). Two others, Ancestry DNA and Family Tree DNA, are limiting their service on ancestry. However, ten out of the fourteen companies researched offer services with medical focus including disease, carrier status and drug response.

Besides working with customers many of the companies are also involved in academic research.
The price for DTC services has been rapidly declining and currently varies from around $100 to $1000 for partial screening while Knome charges $5000 for a complete screening.

Almost all of the companies are currently privately held and details on their financial performance are not publicly available. The only exception is deCode genetics, which was publicly listed for some time. The company incurred net losses between $50m to $100m each year until it was delisted in November 2008 and declared bankruptcy one year later. The cost of genome screening is still high compared to the service offerings evaluated, so the assumption is that currently none of the companies is making profits.

Previously, companies merely informed the consumer about their genome (ancestral roots, likelihood of certain lifestyle disease, etc.) More recently, companies have been starting build a variety of services around the information obtained from screening (e.g. consultation, treatment, collaboration with hospitals / physicians, etc.)

Large biotech companies acquired two of the early players in 2012. Amgen acquired deCode genetics for $415m and Live Technologies bought Navigenics for an undisclosed amount. Both companies ceased to offer DTC services after their acquisition.

2. Technology

The human body contains 50 trillion cells. Each cell contains a nucleus and mitochondria. The nucleus contains 99.9% of all genes, and the mitochondria carry the rest. Genes are small parts of long molecule called DNA that fits into a nucleus. Each DNA contains sugar, phosphate and 4 different bases: A, T, G and C - adenine, thymine, guanine and cytosine. The human genetic sequence is a 3 billion letter string of A's, T's, G's and C's (the code of DNA). DNA is further organized into chromosomes. Humans have 23 chromosomes, cows have 30, and a banana has 11 chromosomes! The entire set of humans' 23 chromosomes is called the human genome.

2.1 Current State of the Relevant Technologies

Gene tests (also called DNA-based tests), the newest and most sophisticated of the techniques used to test for genetic disorders, involve direct examination of the DNA molecule itself. Other genetic tests include biochemical tests of gene products, such as enzymes and other proteins, and microscopic examination of stained or fluorescent chromosomes.

In gene tests, scientists scan a patient's DNA sample for mutated sequences. A DNA sample can be obtained from any tissue, including blood. For some types of gene tests, researchers design short pieces of DNA called probes, whose sequences are complementary to the mutated sequences. These probes will seek their complement among the three billion base pairs of an individual's genome. If the mutated sequence is present in the patient's genome, the probe will bind to it and flag the mutation.

Another type of DNA testing involves comparing the human genetic sequence of DNA bases in a patient's gene to a normal version of the gene. Most of the sequence is the same in everyone. It is estimated there are 10 million places in the genome where a single letter of the sequence sometimes differs from one person to the next. These one-letter spelling variations are known as SNPs, (Single

Nucleotide Polymorphisms), often called **snips**. The cost of testing can range from hundreds to thousands of dollars, depending on the sizes of the genes and the number of mutations tested.

2.2 Key Components/Services Needed

The key components and services needed for human genome testing are:

- Easy and convenient genome collection process. This increases consumers' willingness to provide their genome information to obtain the services (Ancestry, Disease, Drug Response, and Carrier Status).
- Good technology at reasonable cost, which encourages more consumers to participate in the genome services.
- Efficient methodology to analyze samples in a timely fashion to extract accurate and useful DNA sequences information.
- A large database with diverse genome information from consumers, which contributes to the field of personal genomics and genetics studies to enhance the database.
- Maintaining the security of this database, as consumers' genomic information is critical.

2.3 Key Aspects of the Technology

Faster turnaround and higher accuracy

Genome decoding involves two very time-consuming steps. The first step, called the synthesis, involves fragmenting the DNA sample into smaller segments and growing these on a fixed surface with various bio-chemical treatments. Once clusters of marked DNA, called bases, have been synthesized, the second step, called scanning, is performed. Most of the workflow and equipment involved in this process relies on a performance metric defined by number of bases read per run. In 2006, Solexa, a venture-backed startup, announced they could read 1G bases per run. By 2011 this had been increased to 600G bases read per run. Each run lasts several days. A 2011 metric from Illumina claims they read 55G bases in one day.

To ensure accuracy and reliability of results from processes that rely on reading information at molecular level, the industry has come to rely on CLIA standards. In 1988, the US Congress passed the Clinical Laboratories Improvement Amendments (CLIA) with a mission to establish high-quality standards for labs working with human samples to ensure accuracy, reliability and timeliness of patient test results. Labs that perform genome decoding are required to be accredited by the CLIA.

Drastic reduction in costs:

Continuous innovation in speed and depth of genome synthesis and sequencing is the main reason costs are decreasing. Over the past decade, the industry had already applied these techniques to decode lower-complexity genomes such as plants, bacteria and viruses. These applications have had immediate financial returns for a lot of industry players, which has fueled the further

reduction of cost. This process is analogous to the chip industry's continuous march to lower cost and higher transistor density.

Limitation of technologies

A lot of emphasis and innovation has gone into the speed and depth of genome sequencing. This has resulted in newer, faster platforms for high throughput genome sequencing. Newer platforms differ in error profiles from previous sequencing technologies. The choice of a platform for a particular sequencing experiment has become ever more significant.

Future trend in the technology

The high throughput genome sequencing has been enabled by confluence of innovations in many industries – microfluidic MEMS, bio-chemicals, massively parallel computation and analytics. We believe that this trend of continuous improvement in speed and depth will continue well into the foreseeable future, which will lead to opportunities in real-time sequencing and improved accuracy.

3. Broad Contextual Factors

There are a number of issues and challenges facing mainstream acceptance of personalized genome testing. Privacy and confidentiality are perhaps the two most critical issues. The reason is simply because of the fact that genetic results are directly related to the person's identity. Given that the genetic database(s) resulting from personalized testing will have no value if it did not include the identity of the DNA donor, a key question facing many of the startups in the area of personalized DNA testing is how to monetize the value of this database without running into issues of privacy and confidentiality. Can these companies release or sell the results to third parties? Loopholes in existing laws might allow this to happen. For example, the Health Insurance Portability and Accountability Act of 1996 (HIPAA) does not prohibit releasing genetic testing results by medical institutions to third parties (as of this moment we are not aware of any subsequent laws that superseded or changed this). A similar issue that warrants a close look is the protections that these databases are afforded when it comes to law enforcement. Are these databases protected in the same way doctor-patient information is protected? Do law enforcement authorities have to obtain a warrant in order to access patient medical records? Most importantly, what is the status of these genetic testing companies in the eyes of the law? Can they be treated like doctors or other healthcare providers in the sense that they cannot be compelled to release patient information without their consent and/or warrants?

With regard to social and ethical issues, there will be temptations to use the knowledge gained from genome testing in order to influence natural processes, i.e. eugenics. Prenatal screening has already been done to determine characteristics generally not considered birth defects, for example, a baby's sex. The rise of designer babies and parental selection for specific traits raises a host of bioethical and legal issues that will dominate reproductive rights debates in the 21st century. Communities and social groups that are inherently religious or conservatives will undoubtedly get involved in the same way they are involved in the birth control and abortion debate. Therefore, adoption of personalized

genome testing will be met with a considerable amount of resistance from these communities and social groups, which in turn will impact the profitability and success of startups in this arena.

The physical risks associated with most genetic tests are generally very small, particularly for those tests that require only a blood sample or buccal smear (a procedure that samples cells from the inside surface of the cheek.) The only exceptions are the procedures used for prenatal testing, which carry a small risk of miscarriage because they require a sample of amniotic fluid or tissue from around the fetus.

Many of the risks associated with genetic testing involve primarily the emotional, social, or financial consequences of the test results. People may feel angry, depressed, anxious, or guilty about their results. This is especially true since genetic testing cannot determine if a person will show symptoms of a disorder shown in his genetic results, how severe the symptoms will be, or whether the disorder will progress over time. Furthermore, there is a lack of treatment strategies for many genetic disorders once they are diagnosed. The potential negative impact of genetic testing has led to an increasing recognition of a "right not to know," not only in the medical profession but also in the personalized genome testing industry. Another contentious issue which may require regulation by federal and/or state authorities is whether the results may, in some cases, reveal information about other family members in addition to the one who is tested. The “right not to know” may need to be extended to family members. If this is the case one must ask how can that be done without violating the privacy rights of the person being tested. Should it be left to the individual or does the testing company has the right to inform them? What is its impact on the patients’ potential offspring?

The financial impacts of personalized genome testing cannot be ignored either. For example, HIPAA explicitly states, “a presymptomatic genetic diagnosis does not qualify as a preexisting condition,” and thereby offers a degree of protection against insurance disqualification to some patients seeking presymptomatic testing. (The authors are not aware of recent changes in recent healthcare law changes that would stop this). Another point of concern is employment discrimination based on genetic information. In 2008, the US Congress passed the Genetic Information Nondiscrimination Act of 2008 (GINA), which clearly prohibits discrimination against qualified individuals with disabilities who work in the federal government (see title II of GINA). However, there is no national law in the US that extends prohibiting the use of genetic testing to determine employment eligibility beyond employment in the federal government.

There are several reasons to discourage people from undergoing genetic testing. These reasons will affect the profitability of the personalized genome testing startups. There are few state level regulations created to protect genome identity, health insurance coverage and employment discrimination. Both federal and state laws must change in order to create complete protection of peoples’ genetic information.

4. Current and New Value Chains

4.1 Applications for Today and the Future

The applications of human genome information today are primarily finding ancestry and connecting genes with disease. Many companies offer relative finder features, which are powerful ways to find and connect with living relatives from all branches of the patient's family tree.

Human genome information can also connect genes with diseases. Today, researchers are designing the technology and methodology to sequence even more genomes. One key initiative is the 1,000 Genomes Project, an effort by researchers from England, China and the USA to sequence and compare the genomes of at least 1,000 people to focus more precisely on variations linked to disease. The Cancer Genome Atlas is also an effort to collect more than 20,000 tissue samples from over 20 cancers and identify cascades of genetic changes that give rise to tumors. Another example of connecting genes with disease is the patent filed by 23andMe (2012), which provides information on human polymorphisms that are associated with Parkinson's disease (PD). Also disclosed are compositions and methods for use in diagnostics, prognostics, prevention, treatment and/or study of PD.

Future applications for human genome information include pharmacogenomics, finding cures for diseases, and preventive care of predictive diseases. Pharmacogenomics is the study of how genes affect a person's response to drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to a person's genetic makeup. Based on today's attempts to connect genes with disease, researchers have found and observed that certain chemistry will hinder or stimulate specific genes of disease, which may ultimately allow scientists to develop cures to said diseases. This breakthrough, combined with pharmacogenomics, could enable preventive measures to prevent predictive disease. If the three categories can achieve breakthroughs, the government can use this technology and genome information to help people understand their metabolism and prevent certain diseases, which has huge potential to reduce national spending on patient care.

4.2 Analysis of Winners and Losers

Companies that wish to win the consumer market of human genome testing services must have the largest dataset with high accuracy and fast genome sequencing capabilities. These capabilities will generate revenue and profits based on selling databases to drug companies to develop next-generation medicine, to research institutes that will investigate human genome applications, and consumers who want to find family relative, cure diseases, and engage in preventive care based on personal metabolism.

Successful companies must also work continuously with DNA testing chip suppliers and DNA sequencing services in order to lower costs and achieve high growth margins. Companies that can

provide more consumer-oriented services will be able to attract more customers and thereby create larger database. Analytics will enable further traction. In general, companies with an ecosystem of suppliers and partners will be able to lower costs and provide more end services.

The final and most critical criterion that will enable companies to win is having a solid and systematic approach to protecting personal genome information. This will encourage more consumers to participate in and purchase their services. Without well-protected personal privacy boundaries, it will be impossible for a company to be sustainable.

4.3 Likely Strategies/Possible Outcomes

We see human genome testing as a new wave in biogenetics. Similar to how the Internet revolutionized aspects of the human lifestyle, we believe that genome testing carries equivalent potential once the technology matures and becomes more accurate. There will be more vertical applications available from DNA testing in the field of forensics, personnel identification, and etc.

Another area of new opportunities is customized health care, from customized health insurance packages to customized drugs that allow patients to avoid side effects. Broker companies that can help relate genome sequence to best insurance packages could be another offshoot of this change. Targeted marketing of certain drugs for preventative care and for insurance packaging will become more prevalent.

While these are definitely value-adding services, data privacy and misuse of personal genome data will undoubtedly be problems. We expect compliance standards like PCI for the payment card industry to be developed to ensure that data stored by above companies, hospitals and insurance companies remains secure. We may also see firms with the key value proposition of ensuring genome data protection emerge.

5. Summary of Predicted Opportunity

The Human Genome Project is now at a stage analogous to where the Internet was in the mid-1990s. Research on decoding is occurring in research institutes and through government-funded projects. Innovation has begun to take off, and advances continue to mechanize the actual test (for example, Illumina makes bead chip and decoding machines.) This continues to decrease the cost of genome testing, making it increasingly more consumable. These efforts will disrupt existing markets while also creating new markets globally.

The current wave of companies like 23andMe and Pathway Genetics that are building the databases of individual genome maps is equivalent of first wave of Internet content companies such as Netscape and Yahoo, which brought the Internet out of universities and into everyday use.

The next wave of development for genome databases is yet to happen, but it will be exploited to cause changes in health care, drug discovery, or other value-add applications.

Further changes include the creation of new markets, similar to how the Internet created e-commerce and online banking. Public companies like Myriad Genetics and Atossa Genetics are developing and marketing diagnostics risk-assessment products focused on certain diseases such as breast and colon cancer. Genetic tests form a significant subset of their offerings. We conjecture that similar companies will exploit the availability of a large genome database from DTC genetic testing companies. It is quite possible that the rapidly declining cost of these tests may disrupt their current business model. This requires further research. In the meantime, companies like 23andMe are making people comfortable with the idea of having genes decoded, and at a reasonable cost. People are currently using this information to discover ancestry, learn of their susceptibility to certain diseases and, to some extent, for the sake of novelty.

The opportunities for the next wave of human genome testing are in pharmacogenomics, finding cures for certain diseases, personalized medicine, preventive care and privacy protection systems.

Appendix I

Table A: Comparison table of 14 companies engaged in genome sequencing

Company	Inception	Country	Whole / Partial	Price	Direct to customer (DTC)
deCODE genetics	1996	Iceland	partial		not after acquisition
Family Tree DNA	1999	USA	partial	289	x
23andMe	**2006**	**USA**	**partial**	**99+12*9**	**x**
Navigenics	2007	USA	partial		not after acquisition
Knome	2007	USA	whole	4998	x
Counsyl	2007	USA	partial		only through physician
Pathway Genomics	2008	USA	partial	100-200	x
bio-logis	2009	Germany	partial	600	x
Genotek	2010	Russia	whole / partial	10000 / 800	x
Xcode Life Sciences	2010	India	partial	185	x
Lumigenix	2011	USA	partial	479	x
Personalis	2011	USA	whole		no
AncestryDNA	2012	USA	partial	249	x
i-gene		Russia	partial	1500	x

Table B: Comparison table of DTC service product portfolios cross 14 companies

Company	Information depth	Ancestry	Disease	Drug response	Carrier status
23andMe	**960K**	**X**	**x**	**x**	**x**
i-gene		X	x	x	x
Pathway Genomics			x	x	x
bio-logis			x	x	x
Knome	3B		x	x	x

Personalis	3B		x	x	x
deCODE genetics	>1M	X	x		
Lumigenix	700K	X	x		
Genotek			x	x	
Counsyl			x		x
AncestryDNA		X			
Family Tree DNA		X			
Navigenics	~1M		x		
Xcode Life Sciences			x		

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Biographies

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