ORIGINAL ARTICLE

The Efficacy of Retail Genomic Testing: A Case Study of 23andMe

Eric Lee

Propelled by the success of the Human Genome Project (HGP) in 2000, there has been a tremendous surge in computational genomic research. Through advanced genomic exploratory mechanisms, a working template of the human genome, with knowledge of spatial gene locations and single nucleotide polymorphisms that correlate to disease states, was established by the HGP. This new and promising front of knowledge concerning the human genome has spurred the commercialization and mass consumer-directed marketing of genetic testing for disease risk predictions. However, as discussed in this critical review of 23andMe, a leading personal genomics company, the collision of personal genomics, nascent interpretation technology, and unregulated retail marketing has raised many concerns in its societal implications and use. Variability issues arise in the interpretation of genomic data, due to omission of the impact of environmental and behavior factors; the lack of standardized testing and disease risk parameters; and the dearth of genetic experts capable of interpreting and utilizing information obtained from these direct-to-consumer genetic testing firms on retail level.

Honored with *Time Magazine's* 2008 Invention of the Year award for "…making personal genomics accessible and affordable," 23andMe, a privately held personal genomics and biotechnology company based in Mountain View, California, has quickly gained the attention of the press, consumers, and scientific community since its birth in April of 2006. With claims to provide consumers an accurate measure of their susceptibility to or existence of specific diseases, traits, and conditions, 23andMe charges $399 for a personal family tree, $429 for a "health" scan, and $499 for both, in its attempt to pioneer retail genomics. By using kits that were ordered online, consumers simply collect saliva at home and send these DNA samples back to the company for analysis and a report of the results in 6-8 weeks.[1]

Though 23andMe has exploded in the media spotlight, with features in the *New York Times* and on Oprah, as well as securing a recent $5.9 million dollar investment from Google, the startup company's history has been marred with warnings, regulation conflicts, and close scrutiny by governmental agencies with regards to its marketing and ethical practice. In 2008, 23andMe received a warning letter from New York State's Department of Health requiring a permit for genetic testing, as well as a physician's authorization for all cases. That same year, California's Department of Public Health issued a cease-and-desist letter to 23andMe barring them from operation until certified by the state and federal government and only after all tests were ordered by physicians. [2] In July of 2010, the Government Accountability Office (GAO) published an investigation of four genetic testing companies, including 23andMe, that concluded the quality of testing was "…scientifically misleading and meaningless". [3] To these claims, 23andMe co-founder Linda Avey states that the company does not perform "diagnostic," but rather "educational" genetic testing. [4] This defense was enough for the State of New York to grant them a practicing license, but leaves the lingering question of whether one's medical history and disease predilections can ever be purely educational if 23andMe recommends consulting a physician for follow-up after receiving test results.

23andMe contracts out their genomic work to CLIA-certified laboratories that utilize Illumina technology wherein single nucleotide polymorphisms (SNPs) are scanned by first replicating the DNA provided from cheek cells in the saliva sample. SNPs, which are defined as variations in a single base position that occur in greater than 1% frequency of the population, can be synonymous and cause no variation to wild type phenotypes, or these SNPs can be nonsynonymous, and result in an altered polypeptide sequence. Because the human genome is 99.9% similar between individuals, the 10 million commonly known SNPs are a major contributor to variation—averaging out gene base pair lengths estimates that there are 50 SNPs per gene. [5] The underlying importance of mapping out the common SNPs lies in correlations that can be drawn between specific changes in the DNA sequence and the susceptibility of disease and/or response to drugs: this frames the fundamental viability of pharmacogenomics. In order for Illumina to analyze SNP variations, DNA chips containing millions of probes are generated, and complementary DNA from the samples' cells base pair and are localized through fluorescent markers. By way of Chip-Sequencing, over 550,000 SNPs are determined by 23andMe.

However, the accuracy and efficacy of 23andMe and other direct-to-consumer genetic testing companies is brought into sharp focus and debate as only a small fraction of the 10 million commonly known SNPs are analyzed by these companies for personal genomic testing. For example, 23andMe only analyzes 550,000 SNPs out of 10 million for disease risk markers, and as the number of SNPs analyses increase, so does the price tag on tests. Another huge issue in terms of accuracy in disease risk prediction is how these specific fractions of SNPs are chosen, as it is not standardized across leading personal

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genomics companies and can lead to contradictory risk profiles with the same sample of DNA. These contradictions can be attributed to the fact that the companies analyzed different genetic "markers" in assessing the donors' risk for disease. As described in a recent article published in the science journal Nature, researchers determine which markers occur more frequently in patients with a specific disease by conducting "genome-wide association studies, which survey hundreds of thousands or millions of markers across control and disease populations". [3] Direct-to-consumer companies like 23andMe use these publicly available studies to decide which markers to include in their analyses, but none of the companies use the exact same markers in its tests for the same diseases. The GAO stated that 23andMe, as well as the three other leading genomic testing companies investigated, misled consumers by providing test results that were both medically unproven and confounding. For example, one of the results vaguely indicated that a DNA donor was at "significant risk of developing the age-related conditions associated with elevated levels of DNA damage." Another stated that a donor had "faulty methylation patterns" that may lead to "an above-average risk for developing cardiac aging, brain aging, and cancer". [3] In all of the companies interviewed post-investigation, there was a consensus that there is a need for standardization, but differing philosophies and attitudes regarding genomic information prevent such a merge.

In its 550,000 SNP analysis, 23andMe also fails to emphasize that the sequence itself is not the determining factor, but rather its expression; and thus as important outside considerations such as family medical history and environmental factors are not taken into account, there is much room for inaccuracies in disease risk predictions even if standardized genetic marker parameters were developed across private companies. With the still limited scientific knowledge currently available concerning the human genome and its intricate workings, it is almost impossible to predict an individual's real risk for developing such a wide range of diseases and traits as 23andMe claims—over 100—when such important outside factors are omitted by these genomic testing companies. Beyond those concerns, the screening done by 23andMe also does not cater to everyone. The data that 23andMe depends on to pick their SNP markers of interest are mined from clinical studies involving mainly Caucasian research populations and so cannot accurately predict comprehensive risk profiles for any other racial group. Finally, by only screening for SNPs rather than genes, Harvard Medical School's Mark Daley warns, "…you get a potentially dangerously misleading answer." A genomic profile based solely on SNPs cannot be an accurate representation of the entire genomic sequence or include all the most significant markers for disease risk. For example, 23andMe can analyze SNP variants that may slightly elevate breast cancer risk, but because they do not look at whole genes they cannot analyze the presence of distinct genes such as BRCA1 and BRCA2 that vastly increase breast cancer risk. [2]

The above issues involving the accuracy of predictive sequencing analysis directly translate into ethical concerns on the consumer level regarding the utility of the gathered data. As clients of direct-to-consumer genomic testing companies such as 23andMe are directly told that they may have an increased probability of getting certain diseases, unnecessary lifestyle changes and misplaced anxiety may result without warrant. Many experts remain concerned that the medical predictions contained in these results mislead consumers, which has spurred further debate that only physicians should have access to genomic profiles from private sequencing companies. In response, Esther Dyson, a director of 23andMe bluntly claimed, "People can understand statistics about baseball…and I think they ought to understand statistics about genetics". [4] On the other hand, Arthur Beaudet of Baylor College of Medicine stated, "The interpretations of findings that might warrant medical intervention require a level of expertise that is currently beyond the capacity of even most physicians". [6]

In addition to concerns regarding the release of genomic information to consumers and possible misinterpretation, the information itself has become controversial. Due to the sensitive implications of genetic results, the security of patient confidentiality must be approached with extreme care. The ethical management of medical records must be stringently regulated in order to prevent the leakage of private information. Access abuse, which could lead to the unauthorized disclosure of personal information to private or government groups without the permission of the patients, could have dire implications upon the storage of private data. If medical service agencies or insurance companies gained access to private genomic information, unjust screening and compartmentalization of patients into "high and low risk" categories could unfold.

«the [study of the] human genome has spurred the commercialization... of genetic testing for disease risk predictions»

Given the scientific evidence currently available, there are many limitations that personal genomics companies such as 23andMe face in terms of SNP sequencing number and genomic marker standardization for at-risk disease predictions. Equally confounding is the truly variable nature of genetic interpretation as impacted by family medical history, and environmental and behavioral factors. These accuracy issues are compounded by a dearth of expert genetic analysts who are able utilize this information on a retail scale if delivered to a mass consumer market where such testing is easily accessible and affordable. Representatives from multiple personal genomic companies admit that most doctors are not adequately prepared to use direct-to-consumer genetic test information to treat patients. In addition, there is currently no data or other evidence to suggest that consumers have taken steps to improve their health as a result of taking

to-consumer genetic tests. As one expert noted, "even if such information is found to be an especially effective motivator of behavioral change, we're in trouble...because for everyone you find who is at increased disease risk, you'll find another who is at decreased risk. So if this information is actually powerful in motivating behavior then it will also motivate undesirable behaviors in those found to be at low risk". [3]

It is only through the advancement of genomic sequencing techniques, clarification of utility, and stringent monitoring of medical database records that private sequencing companies will be able to navigate through the ethical minefield of determining their societal application. While the importance of genetics in individual medical care shows promise for the future, the usefulness of these direct-to-consumer tests is much debated, and begs the question of whether current genomic interpretation technology is appropriate for retail use in our society today, especially in the delicate arena of personal disease risk prediction.

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On Popularity of 'Body Worlds'

By Emily Clark

The 'Body Worlds' exhibits, which have been on display since 1995, are now the most widely viewed exhibition in the world. Anthropologist Jane Desmond has recently been tackling the question of why. Beyond mere toleration, the exhibit has accrued extraordinary amounts of enthusiasm alongside some controversies. How has this been accomplished? Why do people enjoy it so much? Desmond explains that the way the display is put together grounds the bodies in a context of legitimacy and science - in an effort to inspire wonder rather than discomfort in the visitor. They aren't seen to be people at all. Because the process of 'plastination' removes all identifying features from the person (hair, skin, body fat), they are seen as specimens rather than individuals. No cause of death is ever discernible either. The background, walls covered in images of historical anatomy labs, quotes from philosophers and Renaissance prints, soothes the viewer by saying that to learn from the dead is an honorable and acceptable practice. Plaques thank the people who donated their bodies and ensure that they were given voluntarily. The exhibit was clearly composed in a way that would minimize visitors' unease, and it has apparently been a truly effective method.

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Portrait of an Ostracized Autism Theorist

By Emily Clark

A timely piece addresses the life behind that scientist who, with one research project, initiated a cascade of controversy about whether there was a vaccine-autism link. While the medical establishment has repeatedly discredited Andrew Wakefield's scientific integrity, revoked his medical license and retracted the original 1998 article from the Lancet, he continues to hold a curious position of power. Journalist Susan Dominus visits Wakefield in his adopted state of Texas and witnesses the way he holds sway over families impacted by autism. It is an interesting transformation that she describes from a man who once was a respected physician and researcher to one who is seen in the media as a fraudulent, slippery and unethical appropriator of science for profit, yet who sees himself as a martyr. The image she paints is one of a man devoted to his theories like a preacher is devoted to his beliefs, and who dismisses scientific scrutiny in favor of faith. Wakefield is widely blamed for the current decline in vaccine rates and for scaring parents away from immunizations without adequate evidence. It is easy to see how he's been able to hold this position in the eyes of someone who has seen autism develop in a child. He presents an absolute certainty and trust in the idea that "parents know best". This is something they often don't feel like they get from visits to doctors. As one mother professed, "I think that validation is all that parents want - just that someone is taking the symptoms that we report and looking at them to see what we can do about it." The incidence of autism in children is creeping up nationwide, and without a definitive treatment or any evidence about what parents can do to protect their children, the fact that Wakefield is able to defend his theories just enough to convince parents that he is onto something has huge implications.

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