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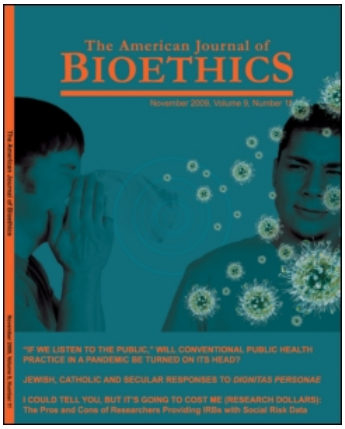

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Social Networking and Personal Genomics: Suggestions for Optimizing the Interaction

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being socialized as governments in the United States and abroad, including those in Australia, the United Kingdom and Canada, bail out private financial institutions to avoid what is perceived to be the even greater social costs of letting them collapse. Regulatory responses to both issues must make private companies accountable for costs so there is a built-in incentive to minimize them.

DTC-PGT instantiates on a small scale the same problem that currently besets economies on a global scale. It is an ethical issue at a clinical level because it concerns a duty of care to people who undergo tests; but it also has political and economic dimensions. Since PGT is marketed globally via the Internet, the costs of lax regulation in one part of the world are potentially exported to other jurisdictions where companies can fly beneath the radar of local regulations. Transnational corporations thus usurp decisional authority that citizens would otherwise exercise through their elected representatives. Such problems are characteristic of a world connected by global markets, and in such a world, bioethics needs to be able to identify and respond to issues on both a micro (local) and macro (global) level.

Marketing tests directly to consumers is not in itself a problem (few people nowadays would think twice about the direct marketing and over-the-counter sale of pregnancy test kits direct to consumers). What is at issue is the evaluation and effective regulation of the product being marketed. PGT provides results that have little or no value as "health information", that influence people in unknown ways, with consequences for their health about which we know nothing. It flouts basic principles of evidence-based medicine, and the costs of inadequate regulation are effectively exported via global markets and the Internet (Human Genetics Society of Australasia 2007).

DTC-PGT has been described as a raid on the medical commons (McGuire and Burke 2008). We agree, and suggest that the appropriate response is a vigorous and multipronged regulatory defense of the medical commons, spearheaded by consumer protection measures. ■

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Social Networking and Personal Genomics: Suggestions for Optimizing the Interaction

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McGuire and colleagues' analysis showing both the social networker's eagerness to explore direct-to-consumer personal genomics and their relative naiveté regarding the usefulness of the current results is potentially troubling. The same web 2.0 enthusiasts who blithely bare their most intimate personal details daily on social networking sites are

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all the more likely to share the results of the personal genomics. Personal genomics now represents technology on the edge of the mainstream, in a similar situation in some respects to the Internet in early 1990s. With barriers to entry plummeting due to technological advances, the current stock of largish, socially responsible purveyors of personal genomic information may give way to direct-to-consumer companies pushing a broader array of less efficacious and more questionable information into the public domain via, among others, social networking sites. This peer commentary will highlight some of the potential pitfalls of personal genomics *vis-à-vis*, personal and extended family privacy concerns, as well as its use of unverified genome wide association studies. It will suggest some simple safeguards that may help both the consumer and the industry from unintended consequences, as personal genomics moves into the mainstream.

The rise of direct-to-consumer genetic testing raises various concerns (McGuire et al. 2007) (Greenbaum et al. 2008) that are amplified in the McGuire and colleagues' (2009) particular demographic—young social networkers. Generalizing, the members of this group are confident and willing to take risks, but may not have yet perfected their risk management skills (Dickerson 2007). And, brought up with pervasive internet access, they tend to be strongly community oriented and trusting of others, but may have novel but skewed views of privacy, providing social websites with their personal, financial, medical and real-time localization information. (Fogel et al. 2009)

As this population grows and is targeted by advertising for direct to consumer genomics, the industry will itself change, further fueling ethical and privacy concerns. Currently the market is dominated by a number of large responsible players who have, for the most part, done their best to protect the consumer from the many potential pitfalls associated with personal genomics, including privacy concerns and non-actionable genetic information. And, thus far, early adopters, willing to payout thousands of dollars for their genome analysis, tended to be well educated as to the limitations of the technology.

However, sequencing and analysis outsourcing, coupled with considerable biotechnology innovations, growing computer processing power and expanding memory capabilities are pushing personal genomics costs down substantially, opening up new markets (Greenbaum et al. 2008), and eliminating the current barriers to entry, allowing for less responsible actors that may push a broader array of either more damning and/or less efficacious personal genomic information services, with fewer privacy controls. While the current market participants tend to use responsible sequencing laboratories and have shown restraint regarding the information that they divulge to their customers, later entrants may not be as socially conscious.

Further, as the personal genomics business model evolves and companies look to alternatives to the relatively unprofitable simple genetic testing model, there are concerns that these corporations may branch out further into more social networking like applications or alternatively, to the potentially more profitable ventures providing data to consumers on non-medical (e.g. normal genetic variation) or non-actionable genetic predispositions.

Like the developers of the Internet prior to the hyper-exponential growth of the World Wide Web, these earlier participants may not fully appreciate how the current lack of regulation might create legal and moral hazards as the industry expands. That is, the elite scientists and engineers developing the initial Internet standards perhaps did not plan for many of the issues (such as spam or phishing) that arose when it became mainstream. One wonders if a similar situation will shortly confront the personal genomics industry—as the costs of sequencing and computational analysis exponentially fall. To protect those most at risk to being exposed to unhelpful genomic information or from exposing theirs and their families' personal genomic information to the world, we suggest that now is an opportune moment for the industry to adopt guidelines. Although space is limited, we present some suggestions:

GENOME WIDE ASSOCIATION STUDIES

Genome wide association studies (GWAS)—studies that survey common genetic variation in a population by probing a dense and very large set of single nucleotide polymorphism (SNPs) across the entire human genome—are now the standard, albeit relatively new, method of choice for determining gene-disease association for complex non-Mendelian disorders.

Science requires an exquisitely sensitive and robust method to identify most disease-associated genes. Often these genes only provide minor and seemingly trivial influences on the eventual disease phenotype (Altmuller et al. 2001). The technologies incorporated into the current GWAS can provide this degree of resolution.

GWAS provide heretofore-unattainable breadth and resolution to genetic analysis. Using chips spotted with hundreds of thousands of SNPS, researchers can interrogate the nearly 12 million SNPs currently known in the human genome for changes in expression in thousands of individuals, related to the disease in question (Pearson et al. 2008).

Notwithstanding the significant developments in these technologies, most reported novel disease-gene associations, although often hyped by the media are either still unconfirmed or have been sufficiently discredited by follow-on research (Ioannidis 2005; Ioannidis et al. 2008). Additionally distressing, substantial amounts of false and/or misleading data from published association studies nevertheless continue to leach into even the accepted scientific literature (Ioannidis 2003). With these and other concerns in mind, we present a number of standards that could potentially be integrated by the industry.

RELIABILITY, CREDIBILITY, AND PRIVACY STANDARDS

Given the still fluid nature of the GWAS literature, reliability, credibility, and privacy standards should only be used when they can demonstrate an ability to provide consistent, reliable and actionable genetic information to prospective

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parents. Although optimally there would be some sort of gold standard for assessing all GWAS', until such time, personal genomics companies should, as a rule, follow industry and academia guidelines and standards when deciding whether or not the science and statistics behind the discovered gene association merits the incorporation into the library of genetic tests provided to consumers. These standards for review and acceptance will continue to evolve over time.

Consistent and Reliable

There are many opportunities throughout the course of a GWAS to create spurious results. It is important that the underlying methods and mindset of the GWAS be reviewed for systemic problems. A non exhaustive list for consideration include: the study design, nature of the biological and medical information, raw data management, data processing and data analysis, and artifacts, including systematic genotyping errors (Hattersley and McCarthy 2005; Newton-Cheh and Hirschhorn 2005; Page et al. 2003).

Size

To ensure statistically significant associations and avoid false associations, GWAS must be performed on a large sample population (Freimer et al. 2005), preferably on at least two technologies to avoid technological artifacts. (Chanock et al. 2007).

Large sample sizes may be associated with a more experienced research group performing the study less likely to be affected by selective reporting biases (Ioannidis et al. 2003). Nevertheless, these populations should preferentially be analyzed for instances of confounding population stratification—ethnic admixture of subgroups with higher disease prevalence (Freedman et al. 2004).

Nonetheless, extremely large studies may find statistically significant results for even trivial or non meaningful effects (Senn 2001); multiple testing corrections are needed given the large number of tests in a GWAS (Moskvina et al. 2008). Conversely, given that most loci will increase the relative risk of the disease by only a small fraction (Bertram et al. 2007), even larger sample sizes, potentially even in the tens of thousands may be required to effectively find those associations (Khoury et al. 2007).

Controls

Matched controls should be drawn from similar populations with similar genotypes and similar environmental exposures (Manolio et al. 2006). Controls should be genotyped in similar manner, preferably on the same day and on the same plates as the other participants to reduce the chance of experimental, non-biologically relevant, artifacts (Hirschhorn et al. 2005).

Biases

Biases may be limited to the particular study at hand or may even be endemic to an entire particular field. Optimally studies will provide transparency and step-by-step methodology for the accumulation of their evidence and have a clear definition of the phenotypes in question[1] as clinical heterogeneity of the trait studied may play a large rule in confounding results and limiting replicability (Wessel et al. 2007). Note however that all biases cannot be known or ever all ruled out, including reporting biases in which not all the relevant data from the study is provided in the article.

Even small biases may create concerns: the additive effect of many small biases may result in greater than expected error. And, particularly in large sample sizes, even small/subtle effects can result in seemingly relevant yet spurious results. Of particular concern are population stratification and genotyping errors (Ioannidis et al. 2008, Newton-Cheh and Hirschhorn 2005).

Significance of the Statistical Evidence

With only a few of the tens of hundreds of thousands of polymorphisms represented in a genome wide analysis likely to be involved in any one disease, the prior odds of any one variant being associated with a particular disease state is exceedingly low. In these instances many suggest that stringent p values, on the order of 10^{-7} (sometimes referred to as the threshold for genome-wide significance) (Hunter et al. 2007; Risch et al. 1996), be used to provide the requisite confidence levels in the results. Unfortunately, most available studies will probably not adhere to such a stringent value as it effectively creates a large class of false negatives (Curtis et al. 2007; Frayling 2008).

Replication

Even with GWAS of large sample size, false associations can still occur. Independent replication of findings (in contrast to a split sample or two stage design that may retain the inherent biases) remain essential to disease susceptibility reporting for a specific genetic disease. Replication is an integral component; most genotype-phenotype associations resulting from GWAS are unconfirmed in replication studies (Chanock et al. 2007, Hirschhorn et al. 2002).

The parameters of what constitutes an adequate replication are debatable. There are also different types of replication analyses, particularly, biological replications and technical replications-both of which are often necessary. Many journals have provided guidelines and commentary on the subject (Editor 1999; Clark et al. 2005, Freimer et al. 2007; Neale et al. 2004; Todd 2006).

Biological Evidence

Under ideal conditions, biological evidence reinforcing the results should be necessary to confirm an association and GWAS should avoid providing specious retrospective biological justification for the experimental results. As this

1.There may also be concerns that the "criteria for defining phenotypes are altered to achieve statistical significance" thereby lessening the usefulness of the underlying data and the purported results (Chanock et al. 2007).

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stringent requirement might lead to false negatives due solely to the current state of relative biological ignorance, it is suggested that a higher confidence level ought to be required when evaluating those associations that do not have any obvious biological evidence to support them (Hattersley and McCarthy 2005).

Respectable Publication

Clinical laboratories ought to require that any gene-disease correlation study that they use be published a highly respected peer-reviewed journal, and a subsequent further general acceptance for one year by the scientific community.

Actionable

The aims of any service ought to be to provide information consumers that will enable them to make informed decisions regarding their health. While certain genotype-phenotype associations may be highly reliable and the tests for them consistent, not all associations will be actionable: typically the specific allele described will only contribute a tiny portion of the disease susceptibility, or the disease may not be entirely penetrant.

Privacy

Many social networkers are apathetic at best about their personal privacy, in the extreme posting their entire lives online. As society redefines accepted privacy norms, we ought to be cognizant of genetic exceptionalism: unlike any and all other forms of private personal information, our genome contains not only detail as to our own lives, but our close family as well. And unlike other personal information, it is unlikely that we could using current technology effectively fully anonymize the genomic data currently being collected. Perhaps the best option is a moratorium on the facilitation of personal genomic data sharing until a better solution can be found to protect the privacy of unsuspecting personal networkers and their extended families. ■

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Genethics 2.0: Phenotypes, Genotypes, and the Challenge of Databases Generated by Personal Genome Testing

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Companies offering direct-to-consumer personal genetic testing (PGT) provide more than individual genetic results, projections about health risk and information about ancestry—they also make available an opportunity to share genotypic and phenotypic information with others. In the study described in the target article, McGuire and colleagues (2009) chose to begin investigating consumer attitudes toward PGT by surveying individuals who already use the social networking site Facebook, arguing that such individuals would be likely to encounter PGT websites and might be interested in the offered social networking component. Judging by the response—the researchers reached a target of 1080 respondents within 36 hours—such individuals are interested, although only 6% of respondents had already participated in a PGT service. Making similar assumptions about familiarity of use might lead one to postulate that users of web-based social networking sites might also be early adopters of health-related social networking sites such as PatientsLikeMe (available at: www.PatientsLikeMe.com) or of web-based electronic personal health records (ePHRs) such as Microsoft's HealthVault (available at: www.HealthVault.com) or Google Health (available at: www.google.com/health). Writing about "Medicine 2.0" applications, Eysenbach (2008) notes that such ePHR sites support five key functions that will alter how we view health information: social networking, participation, apomediation, openness, and collaboration. PGT adds the dimension of genotypic and phenotypic information collected in large digital biobanks to the mix of web-based, health-related applications and allows for the challenges and possibilities of an interactive 'Genethics 2.0'.

Facebook now boasts 175 million active users, with 15 million individuals updating their sites each day (available at: www.facebook.com/press/info.php?statistics). On joining, people are immediately offered connections to local networks, graduates of the same high schools and colleges, and other potential 'friends'. Personal information can be posted and shared with everyone or with selected friends; photos, videos and links to music or websites can be included. The ethos is that information should be shared and sharable.

PGT companies have also adopted this ethos, albeit as part of a business model. Social networking is a component of services offered by companies such as 23andMe (Mountain View, CA), Navigenics (Foster City, CA), and deCODEme (Reykjavik, Iceland). Each company allows users to give friends and family access to their personal genetic

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