Third-party interpretation of personal genetic data: the tools, users, and implications for policymaking

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Abstract

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Individuals have unprecedented access to their "raw" or uninterpreted genetic data through direct-to-consumer (DTC) genetic testing, research participation, or clinical sequencing. Raw data can be transferred to a growing number of independent, third-party interpretation (TPI) tools online for further analysis and interpretation across the domains of health/wellness, ancestry, and genealogy, yet little is known about who is using these tools, why, and with what outcomes. In this project I examined the tools, users, and implications for policymaking to better understand how the growing access to uninterpreted genetic data and various means to interpret it may unfold. First, I characterized TPI tools and interviewed tool developers, which

revealed heterogeneity across tools in terms of the types of information returned and methods for returning it. Several developers portrayed tools as "bridging to the literature" rather than interpreting users' data, in that tools linked user genotypes to information in publicly available databases of variant annotation and scientific literature. Second, I surveyed over 1,100 DTC genetics testing customers about their use of raw data and TPI tools. I found high rates of data download and use of multiple tools, including across the domains of health/wellness, ancestry, and genealogy. In follow-up interviews, I found that social networking and general curiosity were common reasons for this cross-domain use. Finally, to inform policymakers considering regulation in this space, I described DTC raw data provision and TPI as a distributed, supply chain system and identified scientific and technical aspects of each component in the system to inform policy discussions. I mapped some aspects of the regulatory landscape, focusing on U.S. federal health regulations, and concluded that existing regulatory mechanisms may not cleanly fit either DTC raw data or TPI tools and indeed may be constrained by First Amendment free speech protections. I conclude by summarizing my unique scientific contributions; offering recommendations for how to maximize benefits and minimize harms; and identifying avenues for further research, including to characterize an expanding set of DTC services and TPI tools, explore non-DTC routes to raw data access and TPI tool usage, and examine potential policymaking in a global context.

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LIST OF ABBREVIATIONS

AMA: "Ask Me Anything" (Reddit forum)

API: Application Program Interface

BAM: Binary Alignment/Map

CAP: College of American Pathology

CLIA: Clinical Laboratory Improvement Amendments of 1988

CMS: Centers for Medicare and Medicaid Services

CRAM: Compressed Binary Alignment/Map

DHHS: Department of Health and Human Services

DRS: Designated Record Set

DTC: Direct-to-Consumer

DTC-GT: Direct-to-Consumer Genetic Testing

FDA: Food and Drug Administration

GC: Genetic Counselor

GDF: Genetic Data File

GHR: Genetic Health Risk

GWAS: Genome-wide Association Study

HCP: Health Care Provider

HIPAA: Health Insurance Portability and Accountability Act

NASEM: National Academies of Sciences, Engineering, and Medicine

NCBI: National Center for Biotechnology Information

NGS: Next Generation Sequencing

NHGRI: National Human Genome Research Institute

NIH: National Institutes of Health

PCA: Principal Component Analysis

SaMD: Software as a Medical Device

SNP: Single Nucleotide Polymorphism

STSS: Science, Technology, and Society Studies

TPI: Third-party Interpretation

VCF: Variant Call Format

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This research could not have succeeded without the generosity of my participants (tool developers and users) in sharing their time and experiences with me via interviews and online surveys. I am also grateful to the moderators of the Facebook groups and openSNP newsletter who helped me recruit DTC customers to my survey.

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PREFACE

This project began four years ago with a serendipitous visit to a website called "Interpretome" (now GENOtation, http://genotation.stanford.edu/). Interpretome was developed from a series of classroom exercises for a personal genomics course at Stanford University (Karczewski et al., 2012). The medical and graduate students in the course had the option to get their genomes tested at the direct-to-consumer genetic testing (DTC-GT) company 23andMe so they could better understand and personalize concepts such as genetic risk (Salari, Karczewski, Hudgins, & Ormond, 2013). As part of the course, students downloaded a file of their "raw" or uninterpreted genetic data from 23andMe — or elected to use test data if they had not wanted to submit their own saliva sample.

The Stanford students were tasked with running command line scripts on their raw data, producing genetic risk scores for various traits using disease associations for SNPs (Single Nucleotide Polymorphisms, a single base pair variation in DNA) reported in the scientific literature. As one of the Interpretome developers later told me in an interview, it was difficult for students to run these scripts on the Unix command line given their lack of computer or data science backgrounds. Therefore, the teaching assistants, understandably wanting to avoid providing extensive technical support, built a web interface to run these interpretation scripts, and the Interpretome website was born. When I asked the founding professor of this course why they had made Interpretome a publicly available website, he responded that it never occurred to them to do otherwise — why would they keep it private?

When I stumbled across Interpretome in 2014, I started to wonder what other third-party websites or tools might exist to allow people with their raw genetic data in hand (or on their hard drives, rather) to pursue further analysis of their DNA. I was amazed to see Interpretome's feature to create a visualization of genetic ancestry called a PCA (principal component analysis) plot. A PCA plot can illustrate a comparison of genetic ancestry between a target sample(s) and a set of diverse reference populations, pinpointing the target sample(s) in two-dimensional space in relation to the reference

samples. While many DTC-GT companies offer genetic ancestry analyses, I had not previously seen a PCA plot produced “on demand” from consumer data — perhaps because understanding it is not quite as intuitive compared to a percentage breakdown of genetic ancestry provided on a typical DTC report (e.g., an individual is “80% Northern European, 10% sub-Saharan African, and 10% Southern European”). Instead, PCA plots were something I had seen and made often as a research scientist working on genome-wide association studies and general quality control of human genetic datasets. In Interpretome, the PCA plot seemed like more of a research tool made available to the public to "play around with" as they chose. Interpretome was taking a technology and approach to genetic analysis previously concentrated in the ivory tower of academia and bringing it out to the DTC-GT “town square” — a transition that mirrored the growing availability of genetic information more broadly. Indeed, the same technological and statistical innovations that were allowing genetic research to proceed apace, and at a huge reduction in cost, were the same improvements that gave rise to the DTC-GT industry to begin with.

It was clear to me there was a shift underway, in which both the substrates (data) and tools (e.g., PCA) of genetic research were becoming increasingly available to a non-specialist, lay audience. Having worked in academic human genetics research for over a decade, I was concerned that the disdain and dismissiveness for consumer genomics I had frequently seen among genetics professionals would extend into this newer realm of raw data access and third-party interpretation (TPI) tools. This concerned me in part because it could be a missed opportunity for genetics professionals to potentially shape public perceptions of the utility and limitations of genetic information. I also had the related concern that individuals interested in their raw genetic data would increasingly turn to DTC-GT companies over participation in more “traditional,” academic research, as historically the latter has not made raw data available to participants — a concern I articulated in a *Nature* World View commentary (Nelson, 2016). Such a trend could depress participation in research and more generally cede further

ground to DTC-GT companies as “the place to go” for people interested in genetics. This set of concerns prompted me to look deeper into the evolving world of TPI and ideally bring back to my genetics professional colleagues a more complex and considered understanding of why and how people make use of their raw genetic data.

When I started this project, there was seemingly little attention paid to accessibility of raw genetic data and TPI tools, either by journalists or academic researchers. Initially, the primary citation I could give for TPI tools was a blog post from a prominent genetic genealogist, Blaine Bettinger (2013). It seemed strange and rather niche that people would download their raw data file from a DTC-GT company and then upload it to assorted websites for further analysis. If people were doing this, as I would hear from my genetics research colleagues, they were probably geneticists, computer programmers, or some other type of professional infophile. However, there was a lack of empirical research to support these assumptions. Perhaps the DTC-GT companies had studied who was downloading raw data and what they were doing with it, but if so, they were not publishing or otherwise publicizing their findings.

However, I had an intuition that it would not be far-fetched to think that people were accessing and using their raw genetic data, in not insignificant numbers, and not just those with professional backgrounds in science or computing. My intuition was based on observations of the growing DTC-GT industry and my familiarity with various strains of citizen science, such as the growing interest in quantified self and self-tracking (i.e., movements focused on self-directed accumulation and interpretation of personal data) and the existence of online initiatives such as Genomera (Swan, 2012) through which users crowdsource their genetic and other data to answer user-generated research questions. It was with this combination of prior observation, curiosity, and fascination with “non-expert” uses of raw, personal genetic data that I began my explorations into the world of third-party genetic interpretation.

INTRODUCTION

The upward trajectory of consumer genomics

By early 2018, an estimated 12 million people had ordered direct-to-consumer genetic testing (DTC-GT), with DTC-GT companies AncestryDNA and 23andMe largely dominating the market (Regalado, 2018). Between Black Friday and Cyber Monday in 2017, AncestryDNA reportedly sold over 1.5 million testing kits, in what news reports half-jokingly predicted to be stocking stuffers (Molteni, 2017). In the past three years, 23andMe has grown from 1 million customers (23andMe, 2015) to 5 million (23andMe, 2018a). In under two years, relative newcomer MyHeritage attracted 1.2 million customers (Zhang, 2018). This seems a far cry from the DTC-GT testing industry of five to ten years ago which, mired in government investigations (SACGHS, 2010) and regulatory scrutiny (Spector-Bagdady & Pike, 2014), seemed like it might not survive. Smaller companies folded and even bigger companies such as 23andMe were threatened, as the 2013 "crack down" by the U.S. Food and Drug Administration (FDA) forced 23andMe to remove health reports for new U.S. customers (FDA, 2013).

Rather than a complete mowing down, however, instead this appears to have been a weeding out period, where the biggest companies emerged stronger than ever. In 2017, 23andMe gained FDA authorization for a new class of "genetic health risk" tests and is now slowly adding disease risk information back to their product (FDA, 2017e). AncestryDNA alone is responsible for 7 million of the 12 million DTC-GT customers (Regalado, 2018). Additionally, new consumer genomics services continue to enter the market, built on new technologies (e.g., sequencing versus array genotyping) and business models, such as Helix's "app store" model wherein customers can purchase different individual applications developed by external companies but centrally offered on the Helix website (Mullin, 2017).

Notably, this surge in DTC-GT popularity is not happening in a vacuum. Since the completion of the Human Genome Project in 2003 ushered in the era of genomics, there has been a rapid increase in the development and integration of genetic technologies across the sectors of research, medicine, and

informatics (e.g., data storage — see Panda et al., 2018). The advent of modern microarray genotyping technology in the early 2000's (Bumgarner, 2013) enabled high-throughput measurement of hundreds of thousands of single-nucleotide polymorphism (SNP) variants across the genome in a single laboratory experiment — a major advancement over the single SNP assays that had been used to date. Genotyping microarrays allowed for the standardization of the genome-wide association study (GWAS) approach in genomic and biomedical research and also became the technology of choice for DTC-GT companies, allowing them to operate at scale and at consumer-friendly price points. Ongoing advancements in sequencing technologies are leading us ever closer to the long awaited "$1,000 genome," a tiny fraction of the price tag of the first genomes fully sequenced in the Human Genome Project (NHGRI, 2016). Use of genomic information to guide the prevention, diagnosis, and treatment of disease is integral to the vision for precision medicine, announced as a key federal priority by President Obama during the 2015 State of the Union address (Collins & Varmus, 2015). In short, it is faster and cheaper to generate genetic data than ever before, and it is no surprise that "genomics hype" has bled into the public sector, perhaps most clearly manifested in the uptake of consumer genomics.

The typical process of DTC-GT can be described as an exchange of physical and informational materials between the customer and the DTC-GT company. In brief, the customer orders the DTC-GT test online and then receives a sample collection kit via postal mail. The customer provides a saliva sample using the company-provided kit and mails it back to the company. The DTC-GT company, or the genotyping laboratory to which they contract out (discussed further in chapter 3), extracts DNA from the saliva sample and measures the DNA at preselected variant sites — those present on the genotyping microarray used by the given company. The company then analyzes different subsets of genotyped variants to provide interpreted reports across a range of categories, namely health/wellness, genetic ancestry, genealogy (matching to relatives in the customer database), diet and fitness, and non-health physical traits. Both 23andMe and AncestryDNA, for example, offer genetic ancestry estimation and

relative finding, while 23andMe additionally offers reports on health risks and non-health physical traits such as eye color and likelihood of mosquito bites. Despite the diversity of interpreted reports available across companies, each major DTC-GT company (23andMe, AncestryDNA, FamilyTreeDNA, MyHeritage, etc.) allows customers to download a copy of their raw genetic data file in addition to accessing the company's interpreted reports. The raw data file is a plain text file listing each genetic variant tested and the individual's genotype (A's, C's, T's, and G's) at those variants.[1] While the number of variants tested varies by DTC-GT company and by genotyping platform, DTC-GT raw data files typically contain between half a million and one million genetic variants.

Third-party interpretation tools

The availability of raw genetic data from DTC-GT has given rise to various web-based, interpretation-only tools where DTC-GT customers can upload or transfer their raw genetic data for further explication and analysis. These tools are called "third-party" given that the other two parties involved are the DTC-GT company and the customer. Third-party interpretation (TPI) tools therefore exist alongside but independent from the DTC-GT companies themselves, and customers are left to identify and use third-party sites without assistance or guidance from the DTC-GT company. The types of analyses done by TPI tools are as varied as those done by the DTC-GT companies, but broadly fall into the categories of health/wellness, ancestry, and genealogy. However, there are significant but often overlooked differences between the operations of DTC-GT companies and TPI tools, perhaps most notably that a TPI tool can function without any physical exchange of biospecimens or genotyping of DNA. No laboratory space, shipping mechanisms, customer relations, or financial transactions are

[1] DTC-GT raw data files are hundreds of thousands of lines and several megabytes in size. Rather than display a small snapshot in this narrative, readers interested in seeing raw data file examples can download files from openSNP, https://opensnp.org/genotypes, and view in any text editor (e.g., WordPad).

inherently required. This lack of overhead means that some TPI tools are run by just a few individuals as a side job or hobby and indeed some are offered at no cost to the user.

The nature of TPI tools, including who develops them and how they work, is explored in further detail in chapter 1. But foundational to understanding TPI is that without it, a raw data file is largely inert: customers can download it but to what end? Like the Stanford medical students using Interpretome, most people lack the scientific or programming expertise to analyze their genomic data unassisted — unless they are human geneticists (e.g., see Glusman et al., 2012). In a small set of pilot interviews from a class project in 2014, I asked DTC-GT customers (identified through personal networks) whether they would be interested in obtaining a copy of their raw data. One interviewee told me, "I don't know how to read it [the raw data]," but that maybe "if there was a key" she could make some use of it. TPI tools act as — albeit imperfect — keys with which DTC-GT customers seek to unlock further information from their genome.

To date, few empirical studies have been published on DTC-GT raw data and TPI tool usage, and these existing studies have often been limited in scope. In an ethical analysis of five TPI websites offering health-related information, Badalato et al. (2017) observed that many of the same ethical concerns previously described for DTC-GT also apply to TPI, namely considerations of clinical utility and validity, informed consent, lack of medical supervision, advertising claims, and data privacy. However, they concluded that compared to DTC-GT, the TPI tools they studied made fewer claims and typically did not retain or share user data, thus potentially mitigating the ethical concerns typically associated with DTC-GT. As noted in limitations, however, this study only examined five TPI tools and was purposefully limited to those returning only health/wellness information. Turning to the tool users, only one survey has been published to date on raw data and TPI tool usage by DTC-GT customers. In 2016, Wang et al. surveyed 312 DTC-GT customers/tool users to determine their motivations to use TPI, how they learned about these services, and the extent and outcomes of sharing TPI information with health care providers

(Wang et al., 2018). They found 40% of respondents were highly motivated to learn about both health and ancestry via TPI, while only 28% and 22% were motivated to learn solely about ancestry or solely about health, respectively. Furthermore, 30% of respondents reported sharing a TPI report with a provider — most often a general practitioner rather than a genetic counselor (GC). While a significant contribution, this survey was limited by a relatively small sample size and a less detailed set of survey questions compared to the survey I report in chapter 2. Two TPI tools have published reports about their own users: DNA.Land, using information collected through routine use of the site (Yuan et al., 2018), and openSNP through a survey of 550 openSNP users (Haeusermann et al., 2017). However, such tool-specific reports do not provide knowledge of how DTC-GT customers are using their raw data more broadly, across a wide range of TPI tools.

Another component of existing TPI literature interrogates the perspectives of health care providers, primarily genetic specialists. In a mixed methods study of GCs, Allen et al. (2018) found that 53% of 85 GCs surveyed had been contacted by a patient with a TPI report. The GCs who saw patients encountered challenges in preparation time, managing patient expectations, and concerns about quality of both raw data and interpretation, further described in follow-up interviews with a subset of 22 GC survey respondents. Moscarello et al. (2018) presented four case studies demonstrating harms of DTC-GT raw data interpretation as observed by genetics specialty clinics, concluding with a call to action for more research on the scale and scope of potential harms to patients. Notably, both of these studies focused on genetics specialists, while the evidence from Wang et al. (2018) and my DTC-GT customer survey reported in chapter 2 indicates that TPI tool users are much more likely to share information with general practitioners and non-genetics specialists compared to genetics specialists. This observation points to the need for further study of non-genetics providers' experiences with patients who bring in TPI tool reports.

The above body of knowledge was critical to building my initial understanding of DTC-GT raw data usage and TPI tools. However, with my project I sought to fill in perceived gaps with a systematic characterization of a broad set of TPI tools, a more detailed survey of TPI tool users conducted on a larger scale, and an analysis of the regulatory landscape that is based squarely in the scientific and technical details of TPI.

The Genomic Reformation

Several broader scientific and societal trends suggest potentially widespread interest in both access to and use of raw personal genetic data. First, there is the concept of democratizing genetic information (Lee, 2013; McGowan, Fishman, & Lambrix, 2010), or reducing barriers to accessing personal genomic information epitomized by DTC-GT. I refer to this phenomenon as the "open access genome," to signify its relation to other openness trends in science, government, software development, and academic publishing, for example. Second, there is an increasingly participatory model of scientific research, where rather than being passive subjects, citizens are involved in the collection and analysis of data, including their own — what social scientist Barbara Prainsack (2011) has called the "participatory turn." Through online platforms such as Genomera and PatientsLikeMe (Swan, 2012), participants become stewards of their own data, genetic and otherwise, as opposed to the one-time, unidirectional transmission of information characteristic of more traditional research. A third relevant trend is the quantified self movement (Neff & Nafus, 2016; Swan, 2013), where people track and collect numerous types of personal data including diet, exercise, and sleep patterns. While initially the activity of a narrow set of individuals, the proliferation of personal tracking devices such as the FitBit and health-related smartphone applications has widened the base of persons engaged in quantified self activities.

Legal scholar Barbara Evans has compared this historic shift towards increasing availability of personal genetic information to the English Protestant Reformation (Evans, 2014b). During the

Reformation, there was significant controversy about translating the Bible into vernacular languages. Critics feared that in bypassing the Church and directly reading the Bible unassisted, the non-clergy layperson would misunderstand and misinterpret scripture. However, enabling individuals to read sacred texts directly allowed them to engage in debate and discourse without an institutional intermediary or authority and was ultimately beneficial (though perhaps not as viewed by the Catholic Church). The Reformation debates echo those about direct access to personal genomic information, as both are controversies about the rights and roles of expertise (Evans, 2014b). DTC-GT alone and as used in combination with TPI places genomic analysis squarely in the hands of individuals who often lack formal education or backgrounds in genetics. Should these non-experts instead be forced to learn about their genomes through professional intermediaries, or do the benefits of direct access (e.g., potential for self-knowledge) outweigh the risks (e.g., misunderstanding and misinterpretation)?

The mere existence of these scientific and social movements, however, does not guarantee that the associated goals of promoting personal autonomy and self-empowerment are being realized. It is dangerous to equate access with empowerment, i.e., just because someone has their data does not mean they are equipped to benefit from it. A corollary can be found in how Facebook responded to the Cambridge Analytica scandal by enhancing users' ability to download the data that Facebook has generated and collected about them (Matsakis, 2018). While this access might give users some sense of transparency and control, in reality it does very little to change the power dynamic between them and what is, according to Statista (2018), the largest social networking site in the world. In some ways, providing users with their data might falsely inflate their trust in the company and ultimately let the company take greater license with users' data (e.g., selling to third parties) without heightened scrutiny from users. Whether a similar phenomenon exists with DTC-GT companies' provision of raw genetic data is an open question, i.e., could the fact that companies enable raw data download engender sufficient goodwill among the customer base to allow the company to sell aggregate customer data to

pharmaceutical companies (e.g., see Servick, 2015) without too much pushback or loss of market share. The Facebook analogy might go even further, in that DTC-GT customers might recognize the power asymmetry that allows the testing companies to profit off them and their data, yet the downsides are not enough to outweigh the perceived benefits of using the service.

The level of interest in genetic and other personal data suggests that DTC-GT companies and TPI tools offer a perceived benefit to customers and users. With this project, I was particularly interested in understanding the perceived value of raw genetic data and the processes through which meaning is obtained from or assigned to it. In an ethnographic study of 23andMe customers, anthropologist Sandra Lee explored the ways in which value is assigned to genetic data and the larger cultural discourse that frames DNA as "biological potential" (Lee, 2013). Lee contends that DTC-GT highlights debates and struggles about the potentiality of DNA, about who is socially and scientifically empowered to "translate biology into promise" and how. My study builds on this idea of biological potential by specifically examining DTC-GT customers' interactions with uninterpreted genetic data, rather than the interpreted reports.

Additional routes to raw data

Consumer genetic testing is not the only way for individuals to access their genetic data; other potential routes include undergoing clinical sequencing or participating in genetic research. Genome and exome sequencing are becoming more common in the clinic (Manolio et al., 2013) and indeed are a key component of implementing precision medicine. In 2014, the Health Insurance Portability and Accountability Act of 1996 (HIPAA) was updated to create a direct access right whereby patients can directly (i.e., without going through their doctor) access their full laboratory records, known as the designated record set (DRS) (U.S. DHHS, 2014). Evans and colleagues have noted this right could potentially allow patients to access vast amounts of raw data from clinical sequencing tests (Evans, Dorschner, Burke, & Jarvik, 2014). Indeed, in subsequent guidance on the direct access right, the U.S.

Department of Health and Human Services (2016) clarified that a HIPAA-covered genomic sequencing laboratory would be required to return upon patient request the full DRS, including "a copy of the completed test report, the full gene variant information generated by the test, as well as any other information in the designated record set concerning the test." While only a small portion of the patient's genome may have been fully interpreted by the sequencing laboratory or clinician — e.g., at the gene(s) relevant to the primary indication for sequencing — additional uninterpreted genetic sequence generated during the test would be available in the patient's DRS. Similar to DTC-GT customers wanting to extract more information from their raw data, these patients could also seek out TPI of their raw clinical sequencing data. Indeed, some TPI tools already accommodate the file format common to clinical and research sequencing (Variant Call Format, or VCF files), and if the market expanded into this area other tools could likely adjust to accepting VCF files as well. In other words, the main reason existing tools are programmed to accept DTC-GT raw data files is most likely because to date those have been the most commonly available formats.

A second route to access raw genetic data is by participating in a research study that allows its return. Returning research results to participants has been the subject of scientific, ethical, and legal debate for some time (e.g., Beskow & Burke, 2010; Bredenoord, Kroes, Cuppen, Parker, & van Delden, 2011; Wright et al., 2017), though the discourse has focused mostly on interpreted results rather than raw data. Some empirical evidence suggests that members of the general public, despite having no particular background in genetics, would want their raw sequence data if they were to participate in a genome sequencing study (Middleton et al., 2015). The popularity of DTC-GT also suggests that people are interested in their genetic information, interpreted or not, even when that information comes with some uncertainty or caveats. A 2018 report from the National Academies of Sciences, Engineering, and Medicine (NASEM) ultimately supported returning results to research participants, though noting the appropriateness and feasibility of returning results vary with study characteristics, the nature of results,

and the interests of participants (NASEM, 2018, p. xxi). Notably, for the purposes of the report, the Committee considered both raw data and interpreted results jointly as "individual research results." What effects the NASEM report will have on actual practice among researchers remains to be seen, but critics have pointed out the recommendations actually create more regulatory hurdles for return of results and therefore contradict the broader message in favor of return (Wolf & Evans, 2018).

The features of raw data return certainly differ across the contexts of DTC-GT, clinical sequencing, and research, including the populations of individuals involved and the scale and quality of raw data. For example, patients and families undergoing clinical sequencing to end a diagnostic odyssey may have far too much else going on in their lives to pursue obtaining and interpreting additional sequence data. On the other hand, they could be highly motivated to seek all available means of understanding and diagnosing a given condition, including raw data access and TPI. Similarly, the likelihood of research participants availing themselves of raw data access is largely unknown, and expressed interest in a hypothetical scenario (Middleton et al., 2015) may or may not translate into the "real world," non-hypothetical situations. The National Institutes of Health "All of Us" 1-million-person precision medicine research cohort (https://allofus.nih.gov/) may provide an opportunity to observe the rate of uptake, given stated plans to return both interpreted results and "primary genomic data" — either the aligned read data (e.g., BAM or CRAM file) or called genotypes in a VCF file. (Notably, providing only the aligned read data would create significant hurdles in seeking out TPI as it would require TPI tools to incorporate genotype calling machinery, a far more complex task than simply parsing called genotypes from a VCF file.) Absent the ability to observe large-scale raw data access and subsequent TPI in these emerging contexts, examining these phenomena among DTC-GT customers provides preliminary insights into these other areas.

Guiding research questions

While DTC-GT has been well-researched over the past decade, with this project I was interested in a related but distinct set of concerns about the acquisition of raw data and its use in TPI tools. Specifically, DTC-GT has previously been examined for psychosocial impacts (Bloss, Schork, & Topol, 2011), regulatory complexities (Caulfield & McGuire, 2012; Green & Farahany, 2014; Hogarth, Javitt, & Melzer, 2008; Vayena & Prainsack, 2013), effects on health behavior (Bloss et al., 2011; Egglestone, Morris, & O'Brien, 2013; Kaufman, Bollinger, Dvoskin, & Scott, 2012), and social networking (Lee & Crawley, 2009). Granted these areas are all relevant and of interest for raw data and TPI as well; however, I would expect them to manifest differently given the distributed nature of the raw data/TPI supply chain (discussed more in chapter 3) and the heterogeneity of TPI tools. My research questions (RQ) and associated hypotheses (H) were as follows:

- RQ1: Which individuals or institutions create TPI tools and what motivates them to do so?
    - H1: Based on my early exposure to TPI tools such as Interpretome and openSNP, I expected most TPI tools to be created by academics from genetics or related fields for the purposes of satisfying their own or their students' curiosities.
- RQ2: What motivates DTC-GT customers to download their raw data and use TPI tools?
    - H2: The same factors that motivate customers to initially seek DTC-GT (e.g., wanting to learn about health/wellness, ancestry, and/or genealogy and relatives) might also motivate them to download data and seek TPI. In addition, users might seek out information not available from DTC-GT companies. In particular, I suspected 23andMe customers who were unable to access 23andMe health reports during the FDA shutdown (between November 2013 and April 2017) were more likely to have downloaded their raw data and sought health information via TPI compared to 23andMe customers outside this time frame.

- RQ3: What characteristics of a DTC-GT customer are associated with higher likelihood of downloading raw data and using TPI tools?
    - H3: Individuals working in science, engineering, and technology fields might be more likely to download data and use TPI tools, but I did not expect these activities to be the exclusive domain of those with these professional backgrounds.
- RQ4: What are the potential harms and benefits of DTC-GT customers downloading data and using TPI tools?
    - H4: Harms could include distress or anxiety from receiving information about heightened risk of disease, whether that information was a false or true positive. Harms could also include downstream consumption of limited health care resources — the "raiding of the medical commons" concern previously raised about DTC-GT testing more broadly (McGuire & Burke, 2008). Benefits could include increasing scientific and genetic literacy, including how disease risk predictions are made.
- RQ5: How should an understanding of the scientific and technical components of TPI, in particular how it differs from DTC-GT, inform policymaking in this area?
    - H5: Some of the same regulatory mechanisms that oversee aspects of DTC-GT might apply to raw data and TPI, namely regulations administered by the FDA (e.g., medical device regulation) and the Centers for Medicare and Medicaid Services (CMS, e.g., laboratory accreditation). However, distinctions between DTC-GT and TPI will need to be considered and will likely complicate attempts to compare current or future regulation of DTC-GT with that of TPI.

Science, Technology, and Society Studies perspective

My approach to these research questions has been informed by completing the University of Washington Science, Technology, and Society Studies (STSS) graduate certificate program alongside my

primary graduate studies in Public Health Genetics. Next I will describe two aspects of STSS scholarship that have informed my approach. As with other technologies, DTC-GT can be viewed as a socio-technical system or "technology practice" comprising three primary aspects: technical artifacts, such as physical tools and machines; cultural contexts, namely beliefs and values; and organizational infrastructure, including political and economic systems (Pacey, 1983). Indeed, STSS scholars have long viewed technology as an entanglement of materiality, practice, and politics (Gillespie, Boczkowski, & Foot, 2014, p. 4). DTC-GT involves several artifacts, all of which are envisioned, created, and used in a complex web of actors and associations. The technical artifacts include sample collection kits (e.g., the 23andMe "spit kits"), genotyping and sequencing technologies (e.g., SNP microarrays and scanners), genotype calls (i.e., the raw data), interpretive algorithms, and the reported interpretations. The actors include DTC-GT customers seeking and using personal genetic information; the customers' family members; DTC-GT companies with their economic, political, and scientific interests; policymakers; TPI tool developers; and health care providers whose patients may bring in DTC-GT reports and data. In my view, the central artifact in this socio-technical system is the raw data file. Without a portable file of genetic data that can be downloaded and uploaded by a user, or accessed via an API (application program interface), there are no TPI systems, and the DTC-GT company becomes the sole interpreter of customer data.

A second area of STSS scholarship I have drawn on is a critique of the idea that data can ever be "raw." This common misconception is built into the very etymology and history of the word "data," which comes from the Latin verb *dare*, meaning "to give" (Rosenberg, 2013). The implication is that data are given from some external, objective source, and notably the early English language instances of the word "data" were primarily in the context of theology and mathematics. As historian Daniel Rosenberg (2013) explains, data were either given from above and were therefore not questioned, or they were given as a set of assumptions before starting a mathematical proof. According to Gitelman (2013), however, "raw" data is an oxymoron because data can never exist pre-factually, independent of human

thought or action. Rather, data must be generated and imagined as such. Applying this concept to my project, genetic data, far from being "raw," are downstream of several physical and intellectual processes. For the consumer, the choice to download their data, in addition to the selection of and engagement with TPI tools, suggests some "imagining" of potential utility and meaning to be extracted from their genotypes.

My own experiences and conversations with those who perform genome sequencing experiments have led me to understand the perceived "rawness" of data as contextual and largely determined by one's vantage point along the chain of producing and using genetic data. For example, as a research scientist working on GWAS, the genetic data that comes to me from a genotyping laboratory (genotype calls) seems fairly raw, because I have not done anything with or to it. But to someone who works in a genotyping or sequencing laboratory, the truly "raw" data is what comes directly off a genotyping or sequencing machine — e.g., for a florescence-based genotyping assay, the measurements of fluorescent intensity. According to Gitelman we would all be mistaken, because there are no "raw" data when we have decided at the outset that there is some value in genotyping or sequencing a person and have also potentially preselected the DNA sites to be measured based on some external information. The implications for DTC-GT customers are that their raw data file is an imperfect representation of their genome for a variety of reasons. It has been shaped and selected by DTC-GT companies, with a complex set of scientific and financial motivations, and by the genotyping array manufacturers, as discussed further in chapter 3. Even if it were a full genome sequence, as consumers often assume it is, there would be biases in sequencing and alignment protocols and calling algorithms such that the genetic data would not have been "given from above" as a purely objective representation of their DNA.

Chapter overviews: the tools, the users, and the policies

Below I briefly summarize the three main chapters in my dissertation, each of which focused on a separate aspect of raw genetic data and TPI. In chapter 1, I first examined the TPI tools themselves using structured content analyses of tool websites to systematically track features such as types of information returned, modes of generating and presenting that information, and privacy and security measures. Next, I interviewed tool developers to better understand their motivations and processes in building these tools. I found tools to be quite heterogeneous in terms of information returned and methods for returning it. Tools were also created by different groups, including academic researchers, commercial companies, and solo citizen scientist/entrepreneurs. Notably, several of the developers I interviewed espoused the idea that rather than interpreting users' data, their tools were simply "bridging to the literature" by linking user genotypes with information in publicly available databases of variant annotation and scientific literature. This chapter was published in the *Journal of Genetic Counseling* in February 2018 (Nelson & Fullerton, 2018).

In chapter 2, I report results from a mixed-methods survey of over 1,100 DTC-GT customers recruited from several social media venues. In the survey, I asked DTC-GT customers about their motivations for pursuing testing, whether they had downloaded raw data (why or why not), and about their use of TPI tools. When designing survey questions, I incorporated knowledge gained during my chapter 1 research on tools and developers. For example, to follow up on developers' ideas about "bridging to the literature" in contrast to interpretation, I asked tool users to rate their level of agreement with statements such as "I received information about my health" and "I received information about my risk of specific diseases." Based on survey responses, I found high rates of data download and use of multiple tools, including across the domains of health/wellness, ancestry, and genealogy. To better understand this cross-domain use, I conducted qualitative interviews with a subset of respondents and found that primary reasons for using tools outside their original scope of interest

included general curiosity, initial lack of interesting findings, and hearing about tools in various online fora (e.g., Facebooks genealogy groups or genetics-related sub-Reddits).

In chapter 3, I present a scientist's perspective on the challenges that policymakers may face when considering regulation of raw genetic data and TPI tools. I first describe scientific and technical details of each component in the distributed supply chain of raw data provision and TPI: genotyping array manufacturers; DTC-GT companies, including the genotyping laboratories to which they contract out; TPI tools; and the variant annotation databases on which many TPI tools rely. I then map some aspects of the regulatory landscape that should be informed by a fuller understanding of these scientific and technical aspects, focusing on potential health-related regulation administered by the FDA and laboratory accreditation overseen by CMS. My perspective on regulation is again informed by my prior empirical research presented in chapters 1 and 2, in which I sought to understand the perspectives and experiences of TPI tool developers and DTC-GT customers/tool users.

In the concluding chapter, I synthesize my research findings across chapters, highlight novel contributions, suggest avenues for future research, and make recommendations for how to maximize benefits and minimize harms from the use of raw personal genetic data in TPI systems.

CHAPTER 1: "BRIDGE TO THE LITERATURE"? THIRD-PARTY GENETIC INTERPRETATION TOOLS AND THE VIEWS OF TOOL DEVELOPERS

Abstract

Patients and health care consumers can obtain access to their "raw," or uninterpreted, genetic data from direct-to-consumer genetic testing companies, researchers, or providers and pursue self-directed analysis via third-party interpretation tools. Yet relatively little is known about the nature of currently available interpretation tools or the motivations of tool developers. I conducted a structured content analysis of 23 third-party interpretation tool websites and supporting information, tracking features such as types of information returned, modes of generating and presenting that information, and privacy and security measures. I additionally conducted qualitative interviews with a subset of 10 tool developers. A majority of tools (16 of 23, or 70%) offered some type of health or wellness-related information, often extracted from publicly available variant annotation databases. Half of those interviewed characterized their activities as "bridging" users to the scientific literature rather than interpretation, for which they gave a variety of scientific, ethical, and regulatory justifications. The scale, heterogeneity, and complexity of information available from third-party interpretation is unprecedented. While developers aim to enlighten and empower tool users, interpretation-free "bridging" to rapidly evolving databases may instead impose burdens on genetic counselors and other health care providers asked to provide further contextualization and explanation.

Introduction

Patients and health care consumers have unprecedented access to their "raw" or uninterpreted genetic data. Direct-to-consumer genetic testing (DTC-GT) has historically been the most common route of access, as many companies — including 23andMe, AncestryDNA, and FamilyTreeDNA — allow customers to download a file of their uninterpreted genotype (typically SNP array) data in addition to the more well-known interpreted reports. However, shifts in policies and norms of genomic research and medicine are creating new avenues for individuals to obtain their uninterpreted genetic data. In the clinical context, for example, the Health Insurance Portability and Accountability Act (HIPAA) direct access right established in 2014 (45 C.F.R. § 164.524) enables patients to access full laboratory records, known as the designated record set (DRS). Access to the DRS for a genomic sequencing test could include uninterpreted sequence data (Evans et al., 2014; U.S. DHHS, 2016). In the research context, national and international conversations note that many participants may want and perhaps deserve access to their individual data generated in the course of research, which may including uninterpreted genetic data (Bobe, n.d.; Lunshof, Church, & Prainsack, 2014; Nelson, 2016; The Precision Medicine Initiative NIH, 2017; Thorogood et al., 2018). Therefore, as potential providers of such data, the genetics community has a professional interest in understanding the myriad ways patients and participants might seek to leverage their uninterpreted genetic information.

One of the most likely pursuits individuals may undertake with their genetic data is self-directed interpretation and analysis via an online third-party service, a heterogeneous collection of which are currently available (Badalato, Kalokairinou, & Borry, 2017; Spector-Bagdady & Pike, 2014; Wang et al., 2018). While most existing tools were created to process raw data files from DTC-GT companies, the model of third-party interpretation, which is independent or "unbundled" from a genotyping provider/service, is not restricted to DTC-GT data. Indeed, many existing tools already accept or plan to accept file formats more common to clinical or research sequencing, such as Variant Call Format (VCF)

files. As has been observed with DTC-GT reports (Bloss, Wineinger, Darst, Schork, & Topol, 2013; Kaufman et al., 2012; van der Wouden et al., 2016), individuals are likely to bring information from third-party interpretation tools to their providers for further explication. Therefore, providers could be doubly implicated: first as enablers of raw data access and second as managers of patients seeking to self-interpret such data.

The aim of this investigation was to characterize the existing landscape of third-party interpretation tools for personal genetic data, with the broader goal of assisting genetics professionals in understanding and anticipating the outcomes of expanding raw data access and third-party tool use. To accomplish this, I conducted a structured content analysis of tool websites and supporting information for 23 tools, complemented by qualitative interviews with a subset of tool developers. My study contributes knowledge of the operations and motivations of current third-party interpretation services, which furthers understanding of how expanding raw data access will affect individuals, families, researchers, and providers.

Materials and Methods

Dataset

Third-party interpretation tools were identified from a range of sources including blog posts (e.g., Bettinger, 2013), web sites ("DNA Testing Reviews," n.d.; ISOGG, n.d.), DTC-GT customer discussion boards, academic conferences (e.g., Erlich, Gordon, Pearson, Shee, & Pickrell, 2015), scientific literature (Greshake, Bayer, Rausch, & Reda, 2014), and from personal and professional networks. To be included, the tool had to (1) enable a user to process or analyze "raw" genetic data from one or more DTC-GT companies, (2) return some type of information to the user, and (3) be active at the time of study (July - December 2016). These criteria encompass some companies that also offer combined genotyping and interpretation services, in addition to interpretation-only products. (For example, the DTC-GT company

FamilyTreeDNA also offers an interpretation-only service called "Autosomal Transfer.") Note criterion (2) excludes tools exclusively focused on crowdsourcing user genotype data for research, such as Open Humans ("Open Humans," n.d.). A total of 23 tools met these criteria and were included in this study.

Content Analysis

Following previous systematic studies of DTC nutrigenomics (Sterling, 2008) and ancestry (Wagner, Cooper, Sterling, & Royal, 2012) tests, I conducted a structured content analysis of third-party interpretation tools identified as described in the previous section. I used a data collection form to annotate tools on a variety of features, including the "natural history" of the tool (i.e., who started the tool, when, and why); types of information available to the user; how the tool generates that information (e.g., what bioinformatics or analytical approaches and database substrates are used); data privacy and security measures; business model/funding; number and types of users; and ability for users to contribute their data (genetic and/or phenotypic) to research activities. I also tracked where tools could process other (non DTC-GT) genetic data file types, such as VCF. Data collection forms were populated primarily from information on the tool websites, supplemented with additional information such as media articles and blog posts by tool developers and users and, where available, interview data (described below).

Interviews

I conducted semi-structured interviews with 10 tool developers associated with 8 different tools (8/23 = 35% of tools represented). I contacted representatives from each tool up to three times, via either email, a contact form on the tool website, and/or social media (e.g., a Facebook or Twitter account associated with the tool). Developers from six tools explicitly declined to be interviewed; others either did not respond to my initial or follow-up communications. Interview questions were designed to supplement and extend the content analysis and therefore covered the same general topics. In particular, I sought deeper understanding of tool developers' backgrounds and motivations in

developing the tools. I also asked developers about their views on regulation of both interpretation-only tools and DTC-GT more broadly. Interviews were conducted remotely — via phone or Skype, recorded, and transcribed. I thematically analyzed interview transcripts using the qualitative analysis software Atlas.ti (v8). Codes were generated inductively from the data, including the "bridge to the literature" code discussed further below.

All research activities were reviewed and approved by the University of Washington Institutional Review Board as minimal risk human subjects research (approval #50238).

Results

Content analysis

The 23 third-party interpretation tools I studied vary significantly across multiple domains, including how user data are provided to the tool, types of information returned to users, and processes for generating and presenting that information. The tool features discussed below are summarized in Table 1.1. Additional information is presented in Table 1.2, including tool website URL, start year, and whether the tool offers bundled genotyping plus interpretation in addition to the interpretation-only service.

User data: input formats, retention and sharing

Per study inclusion criteria, all tools process uninterpreted genetic data from at least one major DTC-GT company (see "Input formats" in Table 1.1). While 14 tools require the user to have downloaded a genetic data file (*GDF*) to provide it to the tool, 9 offer 23andMe customers the option of transferring their genotypes via the *23andMe API* (application program interface). Five tools accept the *VCF* format common to sequencing data.

The retention and sharing of user genotype data varies between tools. For four tools, user data are *analyzed locally* (i.e., on the user's machine or device), rather than being uploaded to a central

server. The remaining tools centrally process data but store it for varying time periods and purposes. Five tools do *not retain* user data, but rather delete it after a short, pre-defined time period (e.g., after generating and returning a report). Some tools retain data to enable the basic functions of the tool, which involve users collating data: e.g., in GEDmatch to detect and characterize familial relatedness, and in Infinome, to allow users to compare genotypic and phenotypic data with each other. Other tools retain data for research purposes: e.g., in DNA.Land, which conducts academic research internally and with collaborators, and in openSNP, where user data is made publicly available under a Creative Commons (CC0) license. Several tools use aggregated data for internal research and development and *may share* aggregated data with third parties. While most tools' privacy statements preclude sharing of individual-level data without user consent, the sharing of aggregated or de-identified user data is often done without express user permission (i.e., apart from initial agreement to the terms of service or use).

Type of results: genetic ancestry, genealogy and relatives, health and wellness

Similar to the offerings of DTC-GT companies, third-party tools provide three general categories of information to users: genetic ancestry (8 tools), genealogy (5 tools), and/or health and wellness (16 tools), summarized in Table 1.1. Some tools provide information from more than one category. Below I discuss each of these three results categories in turn. Rather than attempt to give an exhaustive list of all available reports, I instead present illustrative examples from each category.

Genetic ancestry information takes a range of forms; however, the most common type of report is a breakdown of *global* (i.e., genome-wide) ancestry composition (provided by six tools). Interpretome offers a slightly different view of global ancestry: a principal component analysis (PCA) plot that pinpoints the user in relation to select reference populations. GEDmatch and Interpretome provide results for *local* ancestry (i.e., ancestry along chromosomal segments), often referred to as "chromosome painting." GPS Origins generates "migration maps" intended to illustrate historical migrations of the user's ancestral groups. Finally, some tools assign mitochondrial DNA, mtDNA

(WeGene, James Lick Haplogroup Analysis) or chromosome Y, chrY (WeGene) *haplogroups*. (Note, while the Chinese company WeGene only provides ancestry reports translated into English, customers who can read Chinese can technically access the health and wellness and relative finder reports available in the full Chinese product, on the same website.)

In the genealogy and relatives results category, information is typically identification and characterization of close relatedness to other individuals who have also provided data to the tool. Three tools offer a *relative finder* feature, which can have an advantage over DTC-GT companies' relative finder tools in that the search space need not be limited to one company's users (e.g., a 23andMe user can find a related AncestryDNA user with GEDmatch). In addition to finding relatives, these tools also present *shared segments* both graphically and numerically (e.g., as total amount of shared centimorgans, cM). David Pike's utilities can perform *haplotype phasing* or generate a list of *shared segments* between either a pair or trio of individuals, but only among individuals for whom the user has data (as analysis occurs locally). Relative information in Enlis Genome Personal is restricted to the ability to track the inheritance of specific variations across family members.

A total of 16 tools provide health and wellness information, which encompasses a variety of subcategories (see Table 1.1). Five tools report on *diet and fitness*, returning results such as carbohydrate sensitivity, antioxidant needs, metabolic efficiency, aerobic potential, and injury risk. Six tools return *pharmacogenetics* information, namely genetic effects on medication response, dosage, and side effects. Two of these tools, Genetic Genie and NutraHacker, provide "detoxification" reports primarily consisting of user genotypes at variants in cytochrome P450 (CYP) genes. These two also provide *methylation* reports: variations in *MTHFR* and other methylation pathway genes. Twelve tools return results on various *traits:* personality and/or physical features. For example, DNA.Land's trait section includes eye color and educational attainment, though developers note additional trait reports are forthcoming (Aufrichtig & Yuan, 2016). DNA Doctor includes a "mental make-up" section with results

on novelty seeking and anxiety, while GENETIConcept advertises a "well-being" section on neurotransmitters and brain function. Two tools (DNA Doctor and NutraHacker) also provide *carrier status* results. *Complex disease* information is provided by nine tools, ranging from information on a few conditions to several thousand.

A caveat to the above subcategorizations is that the range of health and wellness results provided by some tools (notably Promethease, openSNP, LiveWello, and Golden Helix Genome Browser) is determined by the databases that populate their reports (see next section), making it challenging to assign available results into predefined subcategories. To illustrate, as entries are added to the crowd-sourced annotation wiki SNPedia, so will the information available from Promethease and openSNP expand. LiveWello's reports are similarly dynamic due to the "SNP Sandbox" feature, where users can create and share gene report templates with other users, incorporating any genotyped SNP with an assigned reference SNP ID (rsID) (LiveWello, n.d.).

Moreover, there is a broad range of ways in which tools present information across these health and wellness subcategories, largely due to the type of analysis performed. For example, several tools just display user genotypes alongside SNP-level information extracted from publicly available variant annotation or publication databases, as noted above, with minimal additional contextualization. Other tools go beyond these database linking activities, further processing user data to generate an individualized risk estimate, trait score, and/or recommended course of action, discussed further in the following section.

Analysis of user data: types and sources

Next, I discuss the types of analyses tools employ to generate users' results, as well as the information sources used. In Table 1.1, I annotate whether analysis types are peer-reviewed, proprietary, or "homegrown" (i.e., developer's methodology not clearly marked as proprietary). For tools that return health and wellness results, I further indicate whether the analysis involves aggregating

across SNPs, contextualizing against other users' data, and/or making recommendations. In the table, "database linking" is used to describe analyses that simply link user genotypes to external information sources without further processing or curation.

Tools that analyze genetic ancestry typically adapt existing, *peer-reviewed* methodology (e.g., principal component or admixture analysis) to generate reports, though some companies are founded on novel and *proprietary* algorithms — for example, GPSOrigins (Elhaik et al., 2014). One analytical feature that distinguishes ancestry tools, and that they often which to be distinguished by, is the *proprietary reference panel* used. For example, WeGene has attracted many international customers with their collection of Asian ancestry reference samples. Tools' proprietary reference panels often include data from some *public sources*, such as the 1000 Genomes Project and the Human Genome Diversity Project. DNA Tribes and FamilyTreeDNA also incorporate customer data into their reference panels.

Genealogy-focused tools rely on standard, *peer-reviewed* methods for estimating relatedness (e.g., identity by descent analyses) or on *homegrown* tools written by the developer(s) (i.e., David Pike's utilities and James Lick mtDNA haplogroup analysis). GEDmatch appears to use a proprietary relative finder algorithm ("GEDmatch Autosomal comparison software") and an assortment of ancestry calculators created by different "citizen scientists." A key difference between genealogy analyses across tools is the search space for finding relatives: tools that analyze data locally (e.g., David Pike utilities) can only evaluate data files the user has collected (e.g., obtained from other individuals). DNA.Land and GEDmatch, on the other hand, centrally store data and therefore can search for relatives across the full user database.

All tools returning health and wellness information rely to some extent on scientific publications and/or publicly available variant annotation databases, such as ClinVar (Landrum et al., 2016), dbSNP (Sherry et al., 2001), and the NHGRI GWAS catalog (Welter et al., 2014). Where the tools differ

analytically is the extent to which they further curate or process these reference sources, such as through in-house *literature review*. At one extreme, tools simply link users to external information sources (described as *database linking* in Table 1.1). For example, Promethease displays user genotypes alongside entries from the crowd-sourced variant annotation wiki SNPedia — the developers' companion project, which is populated from a combination of manual and automated annotation. The results of these database linking activities are typically presented SNP by SNP, showing user genotypes at the selected variant against information extracted from the external database, for potentially thousands of diseases or traits.

Tools go beyond database linking by doing one or more of the following activities: aggregation, contextualization, and/or recommendation. *Aggregation* across variants involves selecting variants to aggregate and selecting an algorithm or formula for performing the aggregation (e.g., weighting SNP-level effect sizes to generate a genetic risk score, or GRS). For example, some DNA Doctor reports generate an overall risk by summing SNP-level risks extracted from SNPedia (low, medium, high), where the set of SNPs has been selected by the tool developer. Interpretome uses a slightly more sophisticated aggregation approach: calculating a GRS using a formula and SNP list from selected scientific publications. *Contextualization* means presenting the user's results in the context of a given population (e.g., other users or a public reference such as HapMap). For instance, DNA.Land and GeneKnot both present the user's trait score or risk estimate in a histogram populated with other user data. A third way tools go beyond database linking is by making *recommendations*: offering advice or suggested actions based on interpretation of the user's genetic profile. The tools making the most recommendations are those returning diet and fitness reports: AnabolicGenes, Athletigen, DNAFit, GENETIConcept, and NutraHacker. The additional curation effort required to aggregate, contextualize, and/or make recommendations leads to these tools typically returning results on fewer traits or conditions as compared to database linking tools.

Table 1.1. Content summary of third-party interpretation tools.

	User Data		Type of Results			Analysis		
Name	**Input formats[a]**	**Retention and sharing**	**Genetic ancestry**	**Genealogy and relatives**	**Health and wellness**	**Types**	**Sources**	**Developer type**
AnabolicGenes	GDF	Retained; may be shared	-	-	Diet and fitness	Proprietary; aggregates and makes recommendations	Lit review	Company
Athletigen	GDF; 23andMe API	Retained; may be shared	-	-	Diet and fitness; traits	Proprietary; aggregates and makes recommendations	Lit review	Company
David Pike's utilities	GDF	None (analyzed locally)	-	Homozygosity; haplotype phasing; shared segments	-	Homegrown	None (self-contained)	Non-specialist/ citizen scientist
DNA Doctor	GDF; 23andMe API	Not retained (data from API analyzed locally)	-	-	Diet and fitness; pharmacogenetics; traits; carrier status	Database linking; aggregates	SNPedia	Company
DNAFit	23andMe API	Retained; may be shared	-	-	Diet and fitness	Proprietary; aggregates and makes recommendations	Lit review	Company
DNA.Land[b]	GDF	Retained; may be shared	Global	Relative finder; shared segments	Traits	Peer-reviewed; aggregates and contextualizes	Lit review; both public and private sources for ancestry and imputation	Academic
DNA Tribes	GDF	Retained; sharing unclear	Global	-	-	Proprietary	Proprietary reference panel	Company
Enlis Genome Personal	GDF; VCF	Not retained (software product analyzes locally)	-	Track variants across family members	Traits; complex diseases	Proprietary	PubMed; privately curated databases	Company
FamilyTreeDNA (Autosomal Transfer)	GDF	Retained; may be shared	Global	Relative finder; shared segments	-	Proprietary (relative finder); peer-reviewed (ancestry)	Proprietary reference panel	Company

GEDmatch	GDF; 23andMe API	Retained; user controls sharing	Global; local	Relative finder; shared segments	-	Proprietary	Proprietary reference panel	Company
GeneKnot	GDF	Not retained	-	-	Traits; complex disease	Database linking; homegrown; aggregates and contextualizes	Lit review; GWAS Catalog	Non-specialist/ citizen scientist
Genetic Genie	GDF; 23andMe API	Not retained	-	-	Pharmacogenetics; methylation	Database linking	Unclear	Company
GENETIConcept	GDF	Retained; may be shared	-	-	Diet and fitness; pharmacogenetics; traits; complex disease	Unclear; aggregates and makes recommendations	Unclear	Company
Golden Helix Genome Browser	GDF; VCF; BAM; FASTA	None (analyzed locally)	-	-	Traits; complex disease	Database linking	Public sources: e.g., dbSNP, ClinVar, GWAS Catalog, dbNSFP, and SIFT	Company
GPS Origins	GDF	Retained; may be shared	Global; migration maps	-	-	Proprietary	Proprietary reference panel, includes public sources	Company
Infinome	23andMe API	Retained; only used internally	-	-	Traits; complex disease	Database linking	GWAS Catalog	Academic
Interpretome	GDF	None (analyzed locally)	PCA; local	-	Pharmacogenetics; traits; complex disease	Peer-reviewed (PCA); homegrown (local ancestry); database linking; aggregates and contextualizes	GWAS Catalog; PharmKGB; PolyPhen; and Lit review. Reference panel includes public and private sources	Academic
James Lick Haplogroup Analysis	GDF; FASTA, GenBank, ASN1	Not retained	mtDNA haplogroup	-	-	Homegrown	PhyloTree	Non-specialist/ citizen scientist
Livewello	GDF; VCF	Retained; user controls sharing	-	-	Pharmacogenetics; traits; complex disease	Proprietary; appears primarily database linking	Lit review; GWAS Catalog; dbSNP	Company

NutraHacker	GDF; 23andMe API	Retained; sharing unclear	-	-	Pharmacogenetics; methylation; carrier status	Unclear; makes recommendations	Lit review	Company
openSNP	GDF; VCF	Retained; publicly available	-	-	Pharmacogenetics; traits; complex disease	Database linking	GWAS Catalog; SNPedia; Mendeley; GET Evidence System; PLoS	Academic
Promethease	GDF; VCF; 23andMe API	Not retained	-	-	Pharmacogenetics; traits; complex disease	Database linking	SNPedia	Academic
WeGene (English version)	GDF; 23andMe API	Retained; may be shared	Global; mtDNA and chrY haplogroup	-	-	Peer-reviewed	Proprietary reference panel, includes public sources	Company

[a]GDF= genotype data file from one or more DTC-GT company; API=application program interface; VCF=Variant Call Format; ASN1=Abstract Syntax Notation One.

[b]Primary DNA.Land tool only. A companion tool, DNA Compass (http://compass.dna.land/), locally analyzes a VCF of imputed data provided by DNA.Land. DNA Compass links to variant-level health and wellness-related databases.

Table 1.2. Additional information about third-party interpretation tools.

Name	URL[a]	Start Year	Offers genotyping service
AnabolicGenes	anabolicgenes.com	2015	Yes
Athletigen	athletigen.com	2014	Yes
David Pike's utilities	math.mun.ca/~dapike/FF23utils	2010	
DNA Doctor	biostatushealth.com/dnadoctor	2015	
DNAFit	dnafit.com	2013	Yes
DNA.Land	dna.land	2015	
DNA Tribes	dnatribes-snp.com	2006	Yes
Enlis Genome Personal	enlis.com/personal_edition.html	2015	
FamilyTreeDNA (Autosomal Transfer)	familytreedna.com/AutosomalTransfer	2014	Yes
GEDmatch	gedmatch.com	2011	
GeneKnot	geneknot.com	2013	
Genetic Genie	geneticgenie.org	2013	
GENETIConcept	geneticoncept.com/23andme.html	2016	Yes
Golden Helix Genome Browser	goldenhelix.com/products/GenomeBrowse	2012	
GPS Origins	homedna.com/gpsorigins	2016	Yes
Infinome	infino.me	2013	
Interpretome[b]	genotation.stanford.edu	2011	
James Lick Haplogroup Analysis	dna.jameslick.com/mthap	2010	
Livewello	livewello.com	2013	
NutraHacker	nutrahacker.com	2013	
openSNP	opensnp.org	2011	
Promethease	promethease.com	2008	
WeGene (English version)	wegene.com/en	2014	Yes

[a]Tool website URL. For brevity, “http(s)” and “www” prefixes are not shown.

[b]At the time of study, Interpretome was located at interpretome.com; the website was later renamed “GENOtation” and subsequently relocated to the website noted here.

Interviews with developers

Tools are created by a diverse set of individuals and entities: non-specialists/citizen scientists (3 tools), commercial companies (15 tools), and academics from genetics or related fields (e.g., bioinformatics — 5 tools). The category "Company" includes some small Limited Liability Companies (LLCs; e.g., Genetic Genie and DNA Doctor); not all companies charge a fee for reports. Interview participants represented all three categories: one non-specialist/citizen science developer, three developers from commercial companies, and six developers representing four academic tools. Here, I briefly describe several high-level themes from the overall interview data, then focus on a subset of results related to developers' views on the purview of their tools.

Interviews with tool developers helped contextualize the content analysis results by illuminating developers' rationales and motivations for how tools generate and present information to users. Several developers, for example, described building the tool they wanted for themselves. Specifically, they were personally unsatisfied with existing platforms for interpretation and/or sharing their own genetic data, including those provided by the DTC-GT companies, and therefore designed a platform to fill the perceived gap. Developers recognized that users vary in their level of expertise or familiarity with genomics, and many assumed the tool interface would accommodate this range by allowing a self-selecting group of users to delve deeper into linked resources. Developers also held complex views of the medical community. Some were frustrated with a perceived underutilization of genomics in health care and saw their tool as a way to allow users to circumvent this. Developers of one tool, however, have instead cultivated a relationship with genetic counselors, with whom they described having a shared mission of increasing genetic literacy in the general public. Example quotes from these themes not discussed in more detail below are presented in Table 1.3.

Table 1.3. Overview of themes and example quotes from interviews with third-party tool developers.

Anonymized participant IDs are given in parentheses following quotes.

Theme	Example quote
Build the tool they want for themselves	"When I saw [DTC-GT raw] data files coming out — well, that's just a data file waiting to be input into a program. Just there wasn't a program yet. But me with my programming ability, my motivation for the genealogy, and these data files becoming available — well, that was just like the perfect storm if you want to put it that way. And I was in the right place at the right time to use the skills that I had to answer questions that I had." (1135)
Perceptions of tool users	[on fielding emails from users] "It's obvious some of these people have read up on it and have tried to understand, but obviously this is for the public, not all of them have degrees in biology or statistics or anything like that. So they obviously don't — they may or may not have a...background in this. But they're interested, and I like seeing those emails." (1005)
Relationship with medical community	"We've had private contacts [with genetic counselors] that then evolved into shared screen sessions where we looked together at data and say, 'Ok, here's what it means to us, what's it mean to you?' And you know, we learn from each other. So we've had private one-on-one sessions with genetic counselors so that we understand better where each is coming from...And ultimately we're both trying to make sense of what's the right thing to tell somebody." (1336)
Views on regulation of third-party tools	"I think when I got into it, there was only very few players in the field, so there was a little bit of concern that maybe I would get a threatening letter from the FDA but...I think they're not as concerned with the third-party interpretation tools as they are with the one who's actually doing the testing." (1077)
Views on regulation of DTC-GT companies	"So, after the FDA letter to 23andMe, it became clear to me that FDA was ignorant. I mean they said, what if a woman chooses to have her breasts removed based on the 23andMe report...the whole idea that anybody would do anything, any kind of surgery based on 23andMe is ludicrous. And the whole idea that they came up with BRCA2 illustrates that they must be ignorant about fundamental aspects of human genetics." (1782)

Notably, several tool developers (5, or 50% of those interviewed) appeared to challenge or reject the idea that their tools perform "interpretation." Instead they characterized tools as a connection to existing scientific literature repositories or annotation databases (e.g., PubMed, ClinVar, SNPedia), acting as what one developer called a "bridge to the literature." By characterizing their activities this way, developers seemed to distance themselves from entities — including the major DTC-GT companies — that provide more personalized, "packaged" information. Specifically, respondents articulated a difference between simply linking genotypes to literature or annotation databases at the level of individual variants (bridging) versus aggregating information across multiple variants to create some type of personalized report or risk assessment (interpreting). Note this distinction was made primarily in the context of providing information related to health and wellness, rather than ancestry or genealogy. The reasons developers gave for bridging versus interpreting fell into three domains: scientific, ethical, and regulatory. Table 1.4 presents a summary of explanations for bridging and the supporting quotes presented below.

Explanations for bridging: scientific

One major justification for bridging was based in an understanding of genetics as a developing field, where the current state of knowledge about genotype-phenotype associations makes it premature to go beyond bridging. By linking users directly to resources such as SNPedia, for example, rather than attempting to further combine or package the information, one developer viewed his tool as more faithfully representing the complexity of the state of the science. "We sort of avoid a high gloss, glitzy, eye candy simplistic view of things, we're really trying to stick very tightly to: this is a bridge to the scientific literature, and if the literature is complex — well, then, your report's going to be complex" (ID 1336).

Some developers commented specifically on the limitations of combining information across SNPs to produce a single score or estimate of disease risk. One developer felt it was premature to try

Table 1.4. Quotes from third-party tool developers on the theme of "bridge to the literature."

Anonymized participant IDs are given in parentheses following quotes.

Explanations for "bridging"	**Example quote(s)**
Scientific	"We sort of avoid a high gloss, glitzy, eye candy simplistic view of things, we're really trying to stick very tightly to: this is a bridge to the scientific literature, and if the literature is complex — well, then, your report's going to be complex." (1336) "I have a certain roadmap for the application that includes giving more complexity in terms of maybe a number. Like, 'here's your risk.' But I don't think the time is yet ripe for that because I don't think the field has matured yet to the point, you know when we can say we've accounted for 95% of the heritable difference of a trait, then I think the time is ripe to give people a number." (1077) "[There are] certainly no prospective or even retrospective studies on SNP profiles to outcomes or anything like that. There's more and more work these days on polygenic risk scores…the problem is…we have not validated that." (1005)
Ethical	"Ethically, we are certainly…aligned with the groups who feel it's improper to do things like summarize SNPs in ways the scientific literature does not offer any evidence to support. And certain companies have done that in the past, or even continue to do it today." (1336) "Basically this is just a database tool is what I'm providing…I want to leave people with an option to go deeper, which I think that's what I've done with the linking each SNP to SNPedia. So that those who want to sort of read the study that was associated with that SNP can go and do so and decide whether it fits — if it holds up to their standard of what a good study looks like." (1077) [Describing tool report] "I cut and pasted the histogram [from the paper] and I decided I want to look up, for the students, I want to look up their score so they can see where they are on the histogram…And there is a teaching tool. So, in this case it's also effective because if you're pretty far off from the middle it means something for you." (1782) "The point of the website is really not to do any interpretation, it's to show you how you would do interpretation. It is really, you know, it is an educational tool." (1005) "I always tend to say that we try and scare away people actively. By putting out like, all the negative things that like might happen even if there is no evidence at all that this has really happened…it's for this reason that we also don't try to do too much analysis to keep people from not thinking there's like a big benefit to openly sharing it, but rather you probably will not get any benefit out of it." (1671)

Regulatory	"They [FDA] don't have a policy and they're not in a hurry to develop a policy. And this is like the worst type of regulation, because if there is a policy at least I know what I can and cannot do. When there is no policy…you have to guess…And you don't get clear answers. We asked them, why Promethease is ok and 23andMe is not ok? They just give you this answer…'Yeah, it's on our radar, but we really don't have a policy right now.' So, how can we decide what to do next? So, right now we decide to go the safe setting not to give any health information. Just fun traits that, you know, well-being, physical traits." (1702) "I definitely didn't want to involve…FDA, so that was another good reason to keep it in the wellness arena, just to be clear liability-wise with the FDA." (1077) [describing tool report] "Here is your SNPs and click here if you want to read a report about this SNP in general, right? And read about what each genotype means…I don't see how it is an interpretation because we basically just put two things, one thing next to each other, we don't fuse them, it's up to the user to fuse if he or she wants to do that." (1702) "I personally think it's kind of a stretch to say that this is somehow giving advice…While we do have the association between the different genotypes and the associations found so far, we are not calculating a report out of it…You can go to each individual variation and look up what's your personal variation and what literature says about it…in that case, even each individual primary publication is somehow then informing people…I think we are a bit too low level, let's say, to actually somehow fall under it [regulations for returning health information]." (1671)

and provide users with a single risk estimate given the small proportion of heritability explained for most complex diseases: “I don't think the time is yet ripe for that because I don't think the field has matured yet to the point…[where you can] give people a [single] number” (ID 1077). Another observed that while polygenic risk scores are mathematically sound, “[there are] no prospective or even retrospective studies on SNP profiles to outcomes…the problem is…we have not validated that” (ID 1005).

Explanations for bridging: ethical

Another class of justifications for bridging was centered in ethical considerations, including enhancing transparency, educating, and avoiding coercion to contribute data. These ethical commitments often stemmed from recognition of the complexities and uncertainties of genetics, similar to the justifications discussed in the previous section. However, the ethical concerns depart from the scientific ones above in that developers reference downstream harms that might arise from providing users with information unsupported by the science. “Ethically, we are certainly…aligned with the groups who feel it’s improper to do things like summarize SNPs in ways the scientific literature does not offer any evidence to support. And certain companies have done that in the past, or even continue to do it today” (ID 1336). Therefore, rather than oversimplify or obscure complexity, this developer seemed to value transparently presenting the complexity in full to users via linking to primary literature. Another developer’s comments expand on this idea: that linking to literature is not only desirable in and of itself, as a faithful representation of the science, but furthermore empowers users with an “option to go deeper.” He elaborated that by linking users’ reports to SNPedia, “those who want to read the study that was associated with that SNP can go and do so and decide whether it fits — if it holds up to their standard of what a good study looks like” (ID 1077).

Bridging to the literature is also valued as a means of educating users, with the goal of increasing overall genetic literacy. One tool, for example, Interpretome, began as a series of classroom exercises to teach medical students about genetics (Karczewski et al., 2012) and is described by its

developers as a “teaching tool” (ID 1782). Specifically, it is meant to show users how DTC-GT genetics companies generate their reports: “The point of the website is really not to do any interpretation, it's to show you how you would do interpretation. It is really, you know, it is an educational tool” (ID 1005).

A slightly different ethical motivation for bridging exists for the tool openSNP, which makes user genotype data freely and publicly available and therefore takes steps to ensure that users weigh risks and benefits carefully prior to use. “I always tend to say that we try and scare away people actively. By putting out like, all the negative things that like might happen even if there is no evidence at all that this has really happened…it's for this reason that we also don't try to do too much analysis to keep people from not thinking there's like a big benefit to openly sharing it, but rather you probably will not get any benefit out of it” (ID 1671).

Explanations for bridging: regulatory

Finally, a third set of reasons to bridge was articulated relative to regulatory concerns. Some developers were uncertain about whether they could be subject to existing regulatory frameworks, and to mitigate such uncertainty reported erring on the side of caution in at least one of two respects: (1) the categories of information returned (i.e., limiting to “wellness” rather than health-related traits) and/or (2) in the way information is presented. As one developer noted, “they [FDA] don't have a policy and they're not in a hurry to develop a policy. And this is like the worst type of regulation, because if there is a policy at least I know what I can and cannot do. When there is no policy…you have to guess…So, right now we decide to go the safe setting not to give any health information. Just fun traits…well-being, physical traits” (ID 1702). Another developer similarly described having “good reason to keep it in the wellness arena, just to be clear liability-wise with the FDA” (ID 1077).

Apart from limiting the categories of results returned, some developers also hedged regulatory uncertainty by trying to formulate the tool as, again, a bridge to the literature. Here developers portrayed bridging (versus interpretation) as less likely to receive regulatory scrutiny, namely that

linking individuals to publications or annotation databases is distinct from providing health-related interpretation or advice. For example, one developer described why presenting user genotypes next to variant records in SNPedia, PubMed, dbSNP, and the GWAS Catalog does not amount to interpretation: “here is your SNPs and click here if you want to read a report about this SNP in general, right?...I don't see how it is an interpretation because we just, you know, we basically just put one thing next to each other, we don't fuse them, it's up to the user to fuse if he or she wants to do that” (ID 1702). Another developer described their tool as “too low level” to fall under FDA jurisdiction; that it was “kind of a stretch to say that [the tool] is somehow giving advice” because while supporting literature is presented, no report is being generated from it (ID 1671).

Discussion

I characterized and analyzed 23 third-party interpretation tools for raw/uninterpreted personal genetic data from DTC-GT, via structured content analysis of tool websites and qualitative interviews with a subset of tool developers. Third-party tools vary considerably with respect to the types of information returned to users, the analytic and bioinformatic approaches used to generate the information, and the level of transparency to users about analysis and interpretation. In interviews with tool developers, I gained insight into the motivations and rationales driving tool design and, in particular, choices of information to return to users. Notably, for many of the tools providing health-related and wellness information, developers challenge the claim that their tool interprets genetic data. Instead, tools are viewed as simply “bridging” the user to the scientific literature, via linking to publication and variant annotation databases.

While in interviews, several developers emphasized the bridging aspects of their tools, my content analysis results and further examination of example tool reports suggest that instead there is a continuum between bridging and interpretation, and several tools in fact are located along this

continuum. This makes sense given that bridging is a stepping stone on the way to interpretation. For example, Promethease reports are generated by linking user genotypes to SNPedia entries and thus exemplify bridging. However, SNPedia entries can include recommended behavior(s). Because the SNPedia entry content varies across variants, and Promethease returns information about thousands of variants, it is difficult to classify the tool overall as purely bridging versus an intermediate between bridging and interpretation. Developers themselves may not have a clear understanding of whether their tool is primarily bridging or interpreting. For example, one of the developers that described theirs as a "database tool" performs aggregation across variants to produce an overall risk. In summary, I have identified a novel distinction between bridging versus interpretation among third-party tools; however, our understanding of these distinctions, and the continuum between them, is likely to evolve as the number and nature of third-party tools and consumer genetics more broadly continues to expand.

Practice Implications

Providers have been grappling with patients' DTC-GT findings for years (Brett, Metcalfe, Amor, & Halliday, 2012; McGowan, Fishman, Settersten, Lambrix, & Juengst, 2014; Powell, Christianson, et al., 2012; Powell, Cogswell, et al., 2012; van der Wouden et al., 2016); however, the scale and complexity of information that may be conveyed from third-party interpretation of raw genetic data is unprecedented and likely to pose significant new challenges for health care providers (Allen et al., 2018; Borry et al., 2017). Specialists such as genetic counselors and medical geneticists are particularly likely to encounter patients with third-party reports. As Kirkpatrick and Rashkin (2017) observe, in the face of growing access to raw genetic data and third-party interpretation services, "the role of the genetic counselor is likely to evolve dramatically." DTC-GT companies' predicted shift from SNP array genotyping to whole exome or genome sequencing will likely contribute to the genetic counselor's expanding role. Specifically, while uninterpreted data files from most DTC-GT companies currently include less than 1 million SNPs assayed by array genotyping, a progression to sequencing technology would enable

customers to download their genotypes at potentially millions of variants. The scale of "raw" data available will coincide with an increased scale of information individuals may seek from third-party tools and other online information sources. Providers, both inside and outside genetic specialties, may be expected to act as a "buffer" between patients and the glut of genetics and other health-related information available online (Murphy, 2009). Of course, it is not clear that providers can or should perform this buffering role, in the face of competing demands on time and resources.

While tool developers may value faithfully representing the complexity of genetics, it is unclear how these "bridging" activities are experienced by users and the health professionals they are likely to consult. One possibility is that the lack of contextualization or explanation of results will confuse and frustrate users and ultimately not deter them from perceiving the reports as medical advice (Badalato et al., 2017). Alternatively, bridging users to scientific literature may empower them to "dig deeper" at their discretion, promoting autonomy and transparency as intended by several developers I interviewed. Furthermore, the lack of additional processing may make it easier for providers to highlight the limitations of the source information, as compared to third-party tools that aggregate or otherwise potentially obscure research findings. Indeed, a recent ethical analysis of third-party interpretation recognized that, while difficult to parse, non-aggregated SNP-level information may ultimately give users a "more realistic perspective of the uncertain nature of multifactorial disease prediction" (Badalato et al., 2017). My results extend that analysis by revealing developers' rationales for bridging, which though partly driven by ethical considerations such as transparency and promoting autonomy, also stem from regulatory concerns.

The complications of when and how to adjudicate third-party interpretations are only likely to intensify for genetics professionals as access to raw data, and available third-party tools, expands. While historically DTC-GT has been the most common route of access, there are at least two major additional ways in which members of the public will be able to access their raw personal genetic data moving

forward: (1) through clinical sequencing tests and the HIPAA direct access right (45 C.F.R. § 164.524) and (2) via participation in research studies that offer raw genetic data to participants. As the supply of raw personal genetic data expands, a growing number of third-party tools are likely to crop up to meet demand. For example, since freezing the dataset for my current study, I have become aware of additional tools, such as Self Decode (www.selfdecode.com) and CodeGenEU (https://codegen.eu).

Study Limitations

Because the range of third-party tools can be daunting, I intend my investigations to facilitate providers' decisions about how and when to respond to patients' third-party reports. However, the information about third-party tools available on their websites is limited and indeed in some cases biased, particularly for proprietary systems. I sought interviews with tool developers to extend and augment information gleaned from third-party tool websites, although not all developers agreed to be interviewed. While I was able to interview three developers of commercial tools, interviewees were biased towards developers from academia, likely reflecting overall familiarity with and willingness to participate in academic research, in addition to having fewer proprietorial concerns. In addition, while I have described the types of reports available across tools in this study, it is difficult to give an exhaustive and detailed list of all available reports in an easily digestible manner (i.e., in Table 1.1). Available reports may have also changed, either expanded or reduced, since the time of study.

Research Recommendations

I have reported on a novel area of user-driven interpretation of personal genetic data via third-party tools. This work is an important albeit preliminary step to further understanding of personal data access across commercial, research, and clinical realms. Currently very little is known about the *users* of third-party tools, including how they perceive and digest the information, and when and how they might try to integrate the information with their health care. Uncertainty also exists about the potential for regulation of third-party, interpretation-only tools (Evans, 2014b; Lucivero & Prainsack, 2015; Spector-

Bagdady & Pike, 2014). While a full discussion of regulatory complexities is outside the scope of the present study, I note that in interviews, several tool developers expressed concern and uncertainty regarding whether and how they might be regulated (e.g., see example quotes in Table 1.3). Regulatory concerns are further complicated by jurisdictional issues that likely arise for web-based services operating across state and national boundaries. Future work should interrogate both the perspectives and experiences of the DTC-GT consumers who are using these third-party tools and the regulatory environments in which third-party tools are operating.

Human Studies and Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. This study was approved by the University of Washington Institutional Review Board as minimal risk human subjects research (approval #50238). Informed consent was obtained from all individual participants included in the study.

CHAPTER 2: "WELL FOR FIVE DOLLARS, WE'LL SEE WHAT IT SAYS": A MIXED-METHODS STUDY ON CONSUMER USE OF THIRD-PARTY GENETIC INTERPRETATION TOOLS

Abstract

The expanding ability to analyze raw genetic data via third-party interpretation tools poses potential concerns for the medical genetics community, including genotype accuracy, potential for false positives or false negatives, reliability of health-related information, and downstream consumption of limited health care resources. With this study, I aimed to understand the motivations, behaviors, and perspectives of tool users, especially those using their raw data to pursue both health- and non-health-related interests. I conducted a detailed survey on raw data access and third-party tool usage among 1,137 direct-to-consumer genetics testing customers recruited through social media. Follow-up interviews were conducted with 10 respondents who used tools to assess health risks as well as ancestry and genealogy. Only 11% of respondents had not downloaded their data. Among downloaders, 94% used at least one tool, most commonly Promethease (63%) or GEDmatch (84%). Over half (56%) used both health-related and non-health-related tools and differed significantly from those who used only one tool type in terms of demographics, DTC tests ordered, and DTC testing motivations. Interviews illustrated how social networking and general curiosity contributed to use of multiple tool types. Even when initially motivated by ancestry and genealogy, consumers frequently also pursue health information in a largely unregulated and rapidly developing suite of third-party tools, raising both challenges and opportunities for the professional genetics community.

Introduction

Individuals have unprecedented access to their "raw" or uninterpreted genetic data, primarily through direct-to-consumer (DTC) testing, which can be analyzed via a heterogeneous collection of online, third-party interpretation (TPI) tools (Badalato et al., 2017; Nelson & Fullerton, 2018). Some evidence indicates TPI may yield negative consequences for patients, providers, and the broader health care system. For example, media reports have recounted individuals receiving distressing results from TPI, which upon clinical confirmatory testing turned out to be false positives (Almendrala, 2018; Hercher, 2018; Kolata, 2018a). These individuals experienced emotional and financial hardship in unnecessary follow-up, often tracing back to errors in the raw DTC genotypes. The growing popularity of DTC testing (Regalado, 2018) coupled with a burgeoning market for TPI will lead to an increase in self-directed analysis of raw genetic data, potentially exacerbating such problems.

For the medical genetics community, concerns about TPI include genotype accuracy, reliability of health-related information, and downstream consumption of health care resources. Most reports to date have illustrated the negative outcomes of bringing TPI results to genetic counselors (GCs) (Allen et al., 2018), genetics specialty clinics (Moscarello et al., 2018), or otherwise leading to follow-up clinical sequencing (Tandy-Connor et al., 2018). However, few studies have reported on the perspectives of the tool users themselves. One survey of DTC customers found a high volume of raw data download and TPI tool use (67%, or 321/478) (Wang et al., 2018); however, the relationship between DTC testing motivations and use of specific tools was not fully explored. Furthermore, that study did not assess users' downstream actions separately by TPI tool, such as sharing with health care providers (HCPs). Some tool developers have surveyed their own users (Haeusermann et al., 2017; Yuan et al., 2018), but this provides limited insight into use of raw data and TPI tools more broadly and does not measure the degree to which users access multiple tools or make distinctions among the tools that they use.

Here I contribute new information about consumers' use of raw genetic data and TPI tools, from the results of a detailed survey of over 1,100 DTC customers and follow-up interviews with a subset of survey respondents. My aim was to better understand users' motivations and behaviors from initial DTC testing through to downstream use of specific TPI tools and resulting follow-up actions. Understanding this full trajectory will help anticipate the scale and scope of potential demands on health care systems, especially as raw data access extends beyond DTC customers to include research participants (Karow, 2018; NASEM, 2018) and patients undergoing clinical sequencing (U.S. DHHS, 2014, 2016). This study contributes novel insights into how DTC customers leverage their raw genetic data in multiple ways, often concurrently, including to learn about health risks, ancestry, and genealogy.

Materials and Methods

Participant recruitment

I recruited survey respondents during October and November 2017 with staggered postings to various social media venues: six genomics-related sub-Reddits, Twitter, and several Facebook groups (four genealogy groups and the DNA.Land page). Early in the two-month period and once per venue, I posted a brief study description and link to the survey, after seeking permission from group moderators/administrators. Additionally, the survey was sent via newsletter to openSNP (Greshake et al., 2014) users and was posted on my academic website (www.myopenreadingframe.com) and the Institute for Translational Health Sciences (ITHS) Participant Portal. Recruitment messages stated eligibility criteria as being 18 years or older and having taken at least one DTC genetic test — i.e., raw data download and TPI tool use were neither mentioned nor required, though some of the groups targeted were oriented towards TPI tools (e.g., Promethease sub-Reddit or DNA.Land Facebook page). The survey was closed after noting a tapering off in new responses and posting final reminders on each recruitment venue.

Survey design and implementation

The survey questionnaire was designed to cover three main topics: DTC testing, raw data download, and TPI tool use. First, respondents were asked which DTC test(s) they had ordered, when, what motivated them to order the test(s), and whether they had downloaded their raw data. Non-downloaders were asked about reasons for not downloading while downloaders proceeded to a series of questions about TPI tools. Respondents who had used multiple tools were prompted to select one on which to base their responses. All respondents filled out a demographics section and were invited to provide contact information for voluntary follow-up interviewing.

I developed survey questions primarily based on my prior study of TPI tools and developers in chapter 1 (also, Nelson & Fullerton, 2018). However, some items were based on existing instruments: motivations for DTC testing were adapted from the PGen (Impact of Personal Genomics) Study baseline survey (Carere et al., 2014), and questions on how the respondent learned about tools were adapted from Wang et al. (2018). A draft instrument was evaluated via cognitive interviewing (Krosnick & Presser, 2010) with six individuals recruited from a combination of my personal and professional networks. The self-administered, online questionnaire was implemented in REDCap (Harris et al., 2009). While the majority of survey questions were fixed response, some open text comment boxes were also included. The survey instrument is available in the Appendix.

Follow-up interviews

I purposively sampled interview participants from among those survey respondents who volunteered for follow-up contact and reported using a specific combination of tools that spanned health, ancestry, and genealogy (Promethease, DNA.Land, and GEDmatch, respectively) — or "crossover" use, described further below. I conducted semi-structured interviews via phone or Skype and had audio recordings transcribed on Rev (www.rev.com). The interview guide comprised six questions focused on gaining a deeper understanding of respondents' timing and motivations to

download data and use multiple types of tools. For example, did respondents start by using GEDmatch with an interest in genealogy and go on to additionally use Promethease and if so, why? Or, conversely, did initial interest in health and use of Promethease eventually lead to use of genealogy and ancestry focused tools as well and if so, why? I conducted a total of 10 interviews, after which point I had observed multiple examples of crossover in each direction (i.e., participants initially using health tools before using non-health tools, and vice versa). Interviews averaged 36 minutes (SD=14 minutes); an interview with one deaf respondent was carried out via email.

Data analysis

Quantitative survey data were analyzed via univariate descriptives, bivariate, and multivariate analyses (i.e., logistic regression) using all available, non-missing data. The total number of potential responses changes between survey sections due to branching logic; sporadic missing answers also affect the count of available responses for any given survey item. Therefore, throughout I report both percentages and counts. All quantitative analyses were carried out in R statistical and graphing software (R Core Team, 2013). The survey dataset and R analysis code are available on openICPSR (http://doi.org/10.3886/E105721V2). I thematically analyzed qualitative survey data from open text boxes in Atlas.ti v8. Interview analysis was also conducted in Atlas.ti v8 and focused on understanding how and why participants came to use tools across the multiple domains of health, ancestry, and genealogy.

This study was approved by the University of Washington (UW) Institutional Review Board as minimal risk human subjects research, protocol #50238.

Table 2.1. Survey respondent characteristics, overall and grouped by type(s) of tools used. For categorical variables, values are given as within-group percentage, excluding NA/missing values from the denominator. Statistical tests of difference are reported for comparison between groups of tool users: users of non-health only tools, crossover users (used both health and non-health tools), and users of health-only tools.

Variable category	**Variable**	**Overall**	**All tool users**	**Non-health only tools**	**Crossover**	**Health only tools**	**p-value[a]**
	Number of respondents	1,137	820[b]	263	458	98	
	Mean age (SD; range)	46.4 (15; 18->89)	46.7 (15; 18-84)	51.8 (14; 18-83)	45.5 (15; 18-84)	39.4 (12; 20-73)	<0.001
Gender	Women (%)	67.4	67.1	69.8	68.7	53.3	0.011
Race (%)	Asian	1.8	1.6	0.9	1.9	2.2	0.061
	Black or African American	1.7	1.6	0.9	2.1	1.1	
	Hawaiian or Pacific Islander	0.1	0.1	0.0	0.2	0.0	
	White	81.6	80.6	76.2	81.7	86.7	
	Other	3.7	4.0	6.8	2.8	2.2	
	Prefer no answer	2.2	2.4	4.7	1.4	1.1	
	Multiple[c]	8.9	9.8	10.6	10.0	6.7	
	Hispanic/Latino (%)	6.7	6.6	8.1	6.0	5.6	0.677
	Lives in US (%)	75.9	74.9	74.5	74.2	78.9	0.485
Max education (%)	Less than high school	1.0	1.1	2.1	0.5	1.1	0.139
	High school graduate or GED	26.1	26.8	27.0	28.1	20.0	
	College degree	41.0	41.3	39.9	42.2	41.1	
	Master's degree	23.1	22.8	21.5	23.2	24.4	
	Doctorate/terminal degree	8.9	8.1	9.4	6.0	13.3	
Occupation (%)	Business, Financial, Management, Sales	14.2	14.2	15.0	15.1	7.8	0.056
	Computer, Engineering, Math	16.9	17.1	16.7	15.5	25.6	
	Life, Physical, and Social Science	9.2	8.2	6.8	7.2	15.6	
	Legal	2.5	2.6	0.9	3.5	3.3	
	Education, Training, Library	14.3	13.6	13.2	15.3	6.7	

	Arts, Design, Entertainment, Sports, Media	4.7	4.6	3.4	5.1	5.6	
	Healthcare practitioner	8.9	8.9	10.3	7.7	11.1	
	Office, Administrative Support	7.7	7.5	6.4	8.8	4.4	
	Construction, Maintenance, Natural Resources	1.9	1.9	2.6	1.6	1.1	
	Production and Transportation	1.5	1.7	2.1	1.6	1.1	
	Other	18.2	19.7	22.6	18.6	17.8	
	Works in genetic research/medicine (%)	5.1	3.8	3.0	2.3	13.3	<0.001
	Participant in genetic research (%)	14.9	16.2	11.5	19.0	15.6	0.021

[a]Comparing non-health only tool users, crossover tool users, and health-only tool users. P-values are from either Chi-square or Fisher exact tests for categorical values and from ANOVA for continuous variables, comparing three groups (non-health only, both, health-only).

[b]Of the 820 respondents who used at least one tool, one respondent reported using only “various R packages” and could therefore not be assigned a tool user group (non-health only; crossover; health only).

[c]Respondents who checked more than one box for self-identified race are counted under "Multiple." Note all American Indian/Alaska Native respondents checked more than one box and are therefore all counted under "Multiple" here.

SD = standard deviation

Results

A total of 1,137 eligible respondents took the survey (see Table 2.1), including 268 respondents (24%) who did not progress to the end of the survey. The most common recruitment venue was Facebook (624/1,137 or 55%), followed by Reddit (357/1,137 or 31%), Twitter (71/1,137 or 6%), and the openSNP newsletter (62/1,137 or 5%). Fewer than 20 respondents were recruited from each of the remaining venues. Below I report patterns of DTC testing and TPI tool use, including respondents' impressions of information received and follow-up actions taken. I then analyze users by categories of TPI tools, focusing on the common phenomenon (56%, or 458 of 819 tool users) of using both health-related and non health-related tools.

Patterns of DTC testing

Respondents reported ordering a range of DTC tests, with 36% (413/1,137) ordering multiple tests: 21% (236/1,137) ordered two tests, 12% (135/1,137) ordered three, and 4% (42/1,137) of respondents ordered four or more. While asked explicitly about 23andMe, AncestryDNA, and FamilyTreeDNA, respondents noted additional tests via an open text box, most commonly MyHeritage (n=37), Living DNA (n=32), National Genographic (n=19), and Genes for Good (n=18). The majority of DTC tests were ordered between 2016-2018 (see Figure 2.1), potentially reflecting a rise in DTC test popularity and/or a recency effect in that those who recently ordered tests were more likely to be active in my online recruitment venues.

The most common motivations for pursuing DTC testing were general curiosity about genetic make-up (936/972 or 96% rated as somewhat or very important) and curiosity about ancestry (922/977 or 94% rated as important; see Figure 2.2). Less common motivations were limited information about family health history (506/972 or 52% rated as important) and other family members pursuing testing (299/969 or 31% rated as important). In free text responses, 20% of respondents (225/1,137) noted additional motivations, which included pharmacogenomics, being adopted, breaking through "brick

walls" in genealogy research, and professional interests (e.g., teaches genetics or is a GC). Notably, 81% of respondents (787/969) rated desire to have their raw genetic data file as an important motivation to pursue DTC testing.

The prevalence of raw data access as a motivation was borne out in the rate of data download: only 26% (252/974) of respondents reported they had not or were unsure if they had downloaded their raw data from at least one of their DTC tests. Of these 252, 148 had downloaded from another DTC test, leaving only 104 (11% of 974) who had not downloaded any of their available raw data files. Demographically, non-downloaders did not differ from downloaders; however, in pursing DTC testing, downloaders were more motivated to find relatives and obtain raw data compared to non-downloaders (see Figure 2.2).

Third-party tool use

A total of 820 respondents who downloaded raw data also reported using at least one tool and formed the basis for subsequent analyses. Most used multiple tools, with 76% (623/820) using two or more (median number of tools = 3, max number = 11). Thirteen tools were specified in fixed-response survey questions, though respondents could note additional tools via free text. The most commonly used tools were GEDmatch (n=688 respondents), Promethease (n=515), and DNA.Land (n=450; see Table 2.2). Additional tools most frequently noted in the open text box were WeGene (n=39), FamilyTreeDNA (n=35), and MyHeritage (n=34).

Respondents' impressions of the information they received varied by tool (see Figure 2.3). Promethease users overwhelmingly agreed they received information about health (171/186, or 92%) and about risk of specific disease (180/186, or 97%). Notably, some respondents indicated receiving information outside a tool's scope: 16% of GEDmatch users (83/505) agreed they received some health information while 37% of Promethease users (69/188) agreed they received results related to ancestry or genealogy. (It is possible some respondents who used multiple tools did not limit responses to the

Figure 2.1. DTC test(s) ordered by date, over 812 survey respondents who indicated an order date (month and year) for at least one DTC test. Bin width is one year, thus the latest order dates are within the timeframe of survey administration (i.e., during or before November 2017).

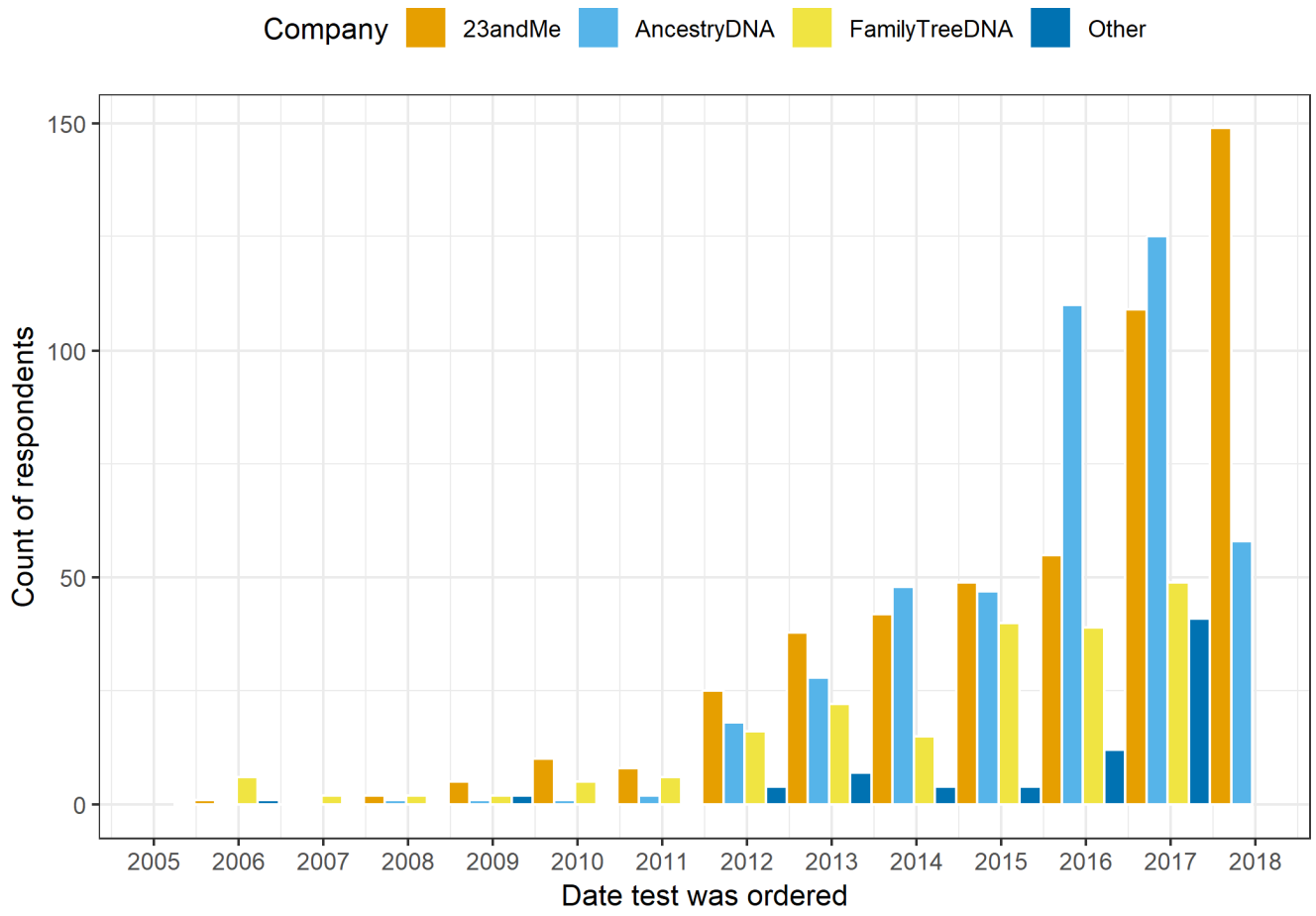


Figure 2.2. DTC testing motivations, separately for those who downloaded data ("downloaders") and those who did not ("non-downloaders"). Counts plotted to the right of x=0 are for endorsement of importance; counts plotted to the left of x=0 are for non-importance. Asterisks indicate motivations that differ significantly (at $p < 0.05$) between downloaders and non-downloaders: ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$. Finding relatives and obtaining raw data were rated more important by downloaders compared to non-downloaders, while participation in research was rated more important by non-downloaders compared to downloaders. The other DTC testing motivations did not significantly differ between the two groups, though these comparisons may be underpowered.

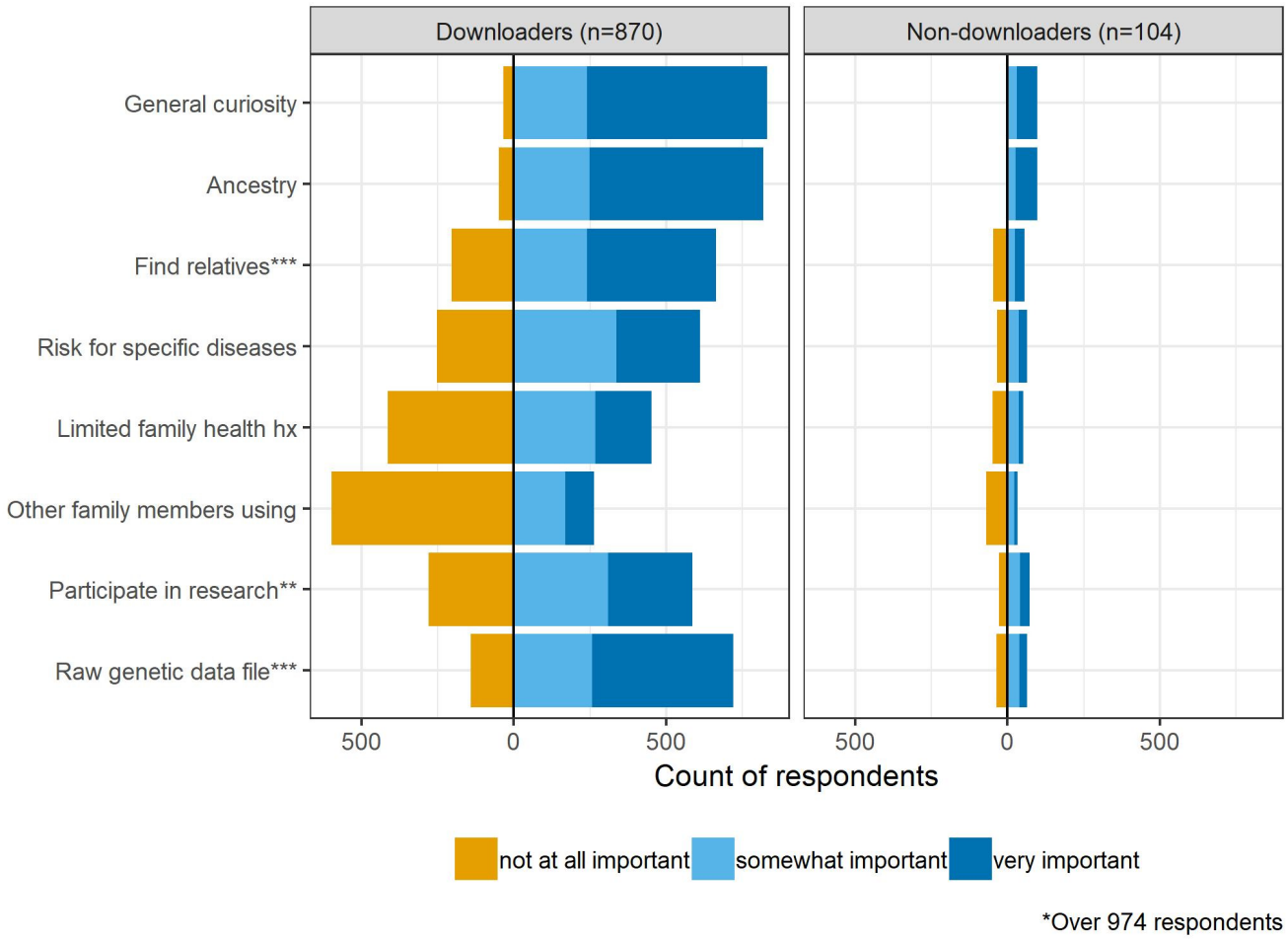


Table 2.2. Third-party interpretation tools used by survey respondents. Includes any tool that at least five respondents reported using, including tools noted in open text box responses. I present counts and percentages of tool user respondents that both (1) indicated using tool and (2) chose to answer survey questions about their use of the given tool (i.e., respondents who had used more than one tool were prompted to select one on which to base subsequent responses). I flag tools that offer some type of health-related information including nutrition, fitness, and other wellness topics, as those designations determined how respondents were categorized into one of three user groups: users of non-health only tools, users of health-only tools, and the crossover group.

Tool	Total users (N, %[a])	Total who selected for responses (N, %[a])	Includes health information[b]	Open text box entry[c]
GEDmatch	688 (83.9%)	505 (61.6%)		
Promethease	515 (62.8%)	188 (22.9%)	X	
DNA.Land	450 (54.9%)	58 (7.1%)		
openSNP	113 (13.8%)	12 (1.5%)	X	
GeneticGenie	60 (7.3%)	4 (0.5%)	X	
Interpretome	54 (6.6%)	1 (0.1%)	X	
Livewello	47 (5.7%)	7 (0.9%)	X	
WeGene	39 (4.8%)	4 (0.5%)		X
Athletigen	35 (4.3%)	1 (0.1%)	X	
FTDNA	35 (4.3%)	1 (0.1%)		X
MyHeritage	34 (4.1%)	2 (0.2%)		X
NutraHacker	27 (3.3%)	1 (0.1%)	X	
Codegen	27 (3.3%)	3 (0.4%)	X	X
DNAFit	15 (1.8%)	2 (0.2%)	X	
Seeq/Gencove	11 (1.3%)	0 (0%)	ND	X
GeneKnot	9 (1.1%)	0 (0%)	X	
Infinome	9 (1.1%)	0 (0%)	X	
DNAGedcom	8 (1%)	1 (0.1%)		X
GenePlaza	7 (0.9%)	0 (0%)	ND	X
Impute.me	5 (0.6%)	5 (0.6%)	X	X

[a]Percentages are given out of 820, the total number of respondents who indicating using at least one tool.

[b]ND: indicates tools that were not categorized as either health or non-health, i.e. tools that essentially offer an "app store" with a dynamic menu of options.

[c]Indicates tools that were noted by respondents in an open text box for "other tool," whereas remaining tools were listed in fixed response survey items.

Figure 2.3. Agreement with statements about information received from TPI tools, separately by tool, over 820 respondents who reported using at least one tool. Counts plotted to the right of x=0 are for agreement; counts plotted to the left of x=0 are for disagreement.

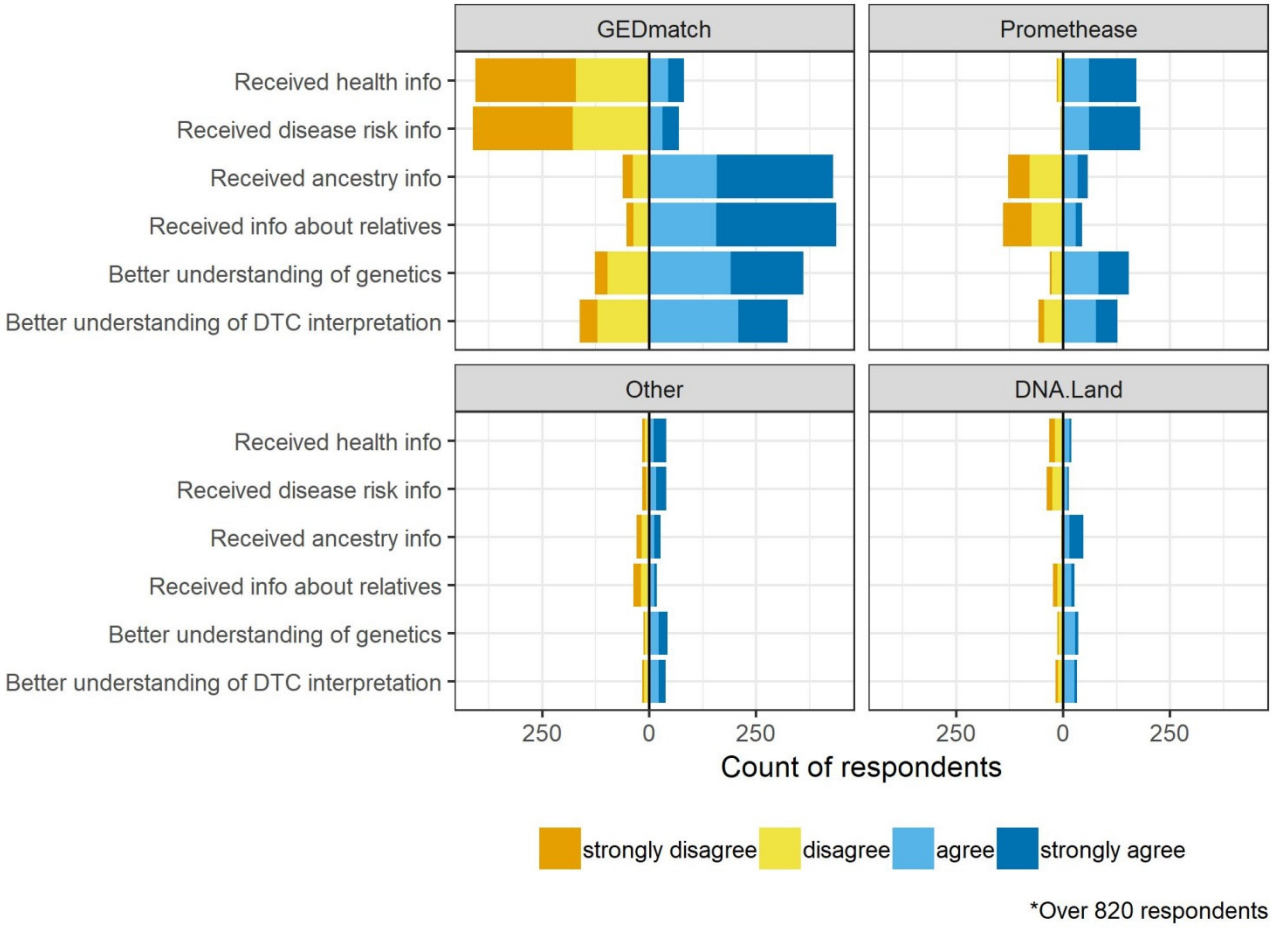
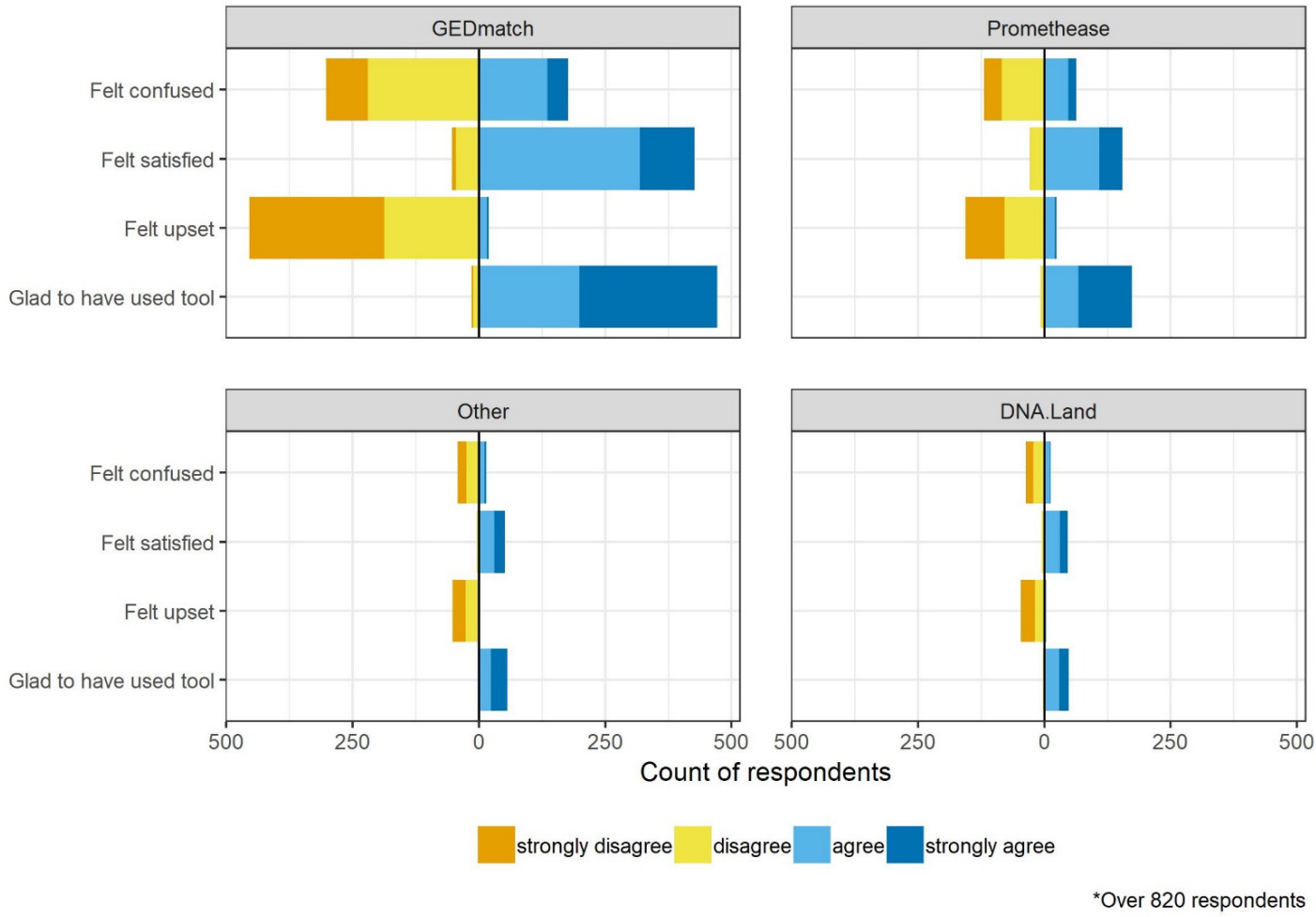


Figure 2.4. Reactions to information received from TPI tools, separately by tool, over 820 respondents who reported using at least one tool. Counts plotted to the right of x=0 are for agreement; counts plotted to the left of x=0 are for disagreement.



selected tool as directed in survey instructions.) Across all tools, respondents largely agreed using the tool increased their understanding of genetics in general (593/778 or 76% agreed) and of how DTC companies interpret genetic data (522/775 or 67% agreed). The majority also felt satisfied with the information received (678/770 or 88%), though some reported feeling confused (266/767 or 35%) or upset (48/758 or 6%). These reactions were relatively consistent across tools (see Figure 2.4).

The most common follow-up actions were sharing the results with a family member (664/780 or 85% shared) or non-family member friend or loved one (552/778 or 71% shared). Other common follow-up included pursuing additional analysis via a different tool (430/776 or 55%), pursing more genetic testing (253/776 or 33%), or participating in a genetic research study (275/775 or 35%). Few respondents made changes to either health insurance (7/770 or 0.9% changed) or other types of insurance (i.e., life or long-term care; 8/771 or 1% changed). Only 15% of respondents (116/775) indicated sharing results with an HCP, most commonly a general practitioner (92/116, or 79% of those who shared). Notably, only 13 respondents (11% of 116) reported sharing results with a medical geneticist or GC. A total of 52 respondents (45% of 116) wrote in an additional type of HCP with whom they shared results, including practitioners from non-genetics specialties (e.g., cardiologist, gastroenterologist, ophthalmologist), psychiatry/psychology, and alternative medicine (e.g., naturopath, acupuncturist). Note when limiting to respondents answering based on Promethease, 29% (56/188) reported sharing information with an HCP.

Categories of third-party tools used

Next, I sought further understanding of what factors influenced an individual to use a given tool or combination of tools, in particular when respondents used multiple tools across the domains of health, ancestry, and genealogy. First, I performed a series of logistic regression analyses using tool use (yes/no) as an outcome, separately for the 7 tools with at least 40 users: GEDmatch, Promethease, DNA.Land, openSNP, GeneticGenie, Interpretome, and Livewello (see Table 2.3). Potential explanatory

variables were each of the eight DTC testing motivations, survey recruitment venue, and DTC test(s) ordered. Curiosity about genetic ancestry was associated with use of GEDmatch (β=0.623, $p<0.001$) and DNA.Land (β=0.358, $p<0.01$), while desire to find relatives was only significantly associated with GEDmatch (β=0.509, $p<0.01$). Desire to learn about personal risk for specific diseases was positively associated with use of Promethease (β=0.659, $p<0.001$), openSNP (β=0.460, $p<0.05$), GeneticGenie (β=0.933, $p<0.001$), and Livewello (β=1.015, $p<0.001$) but negatively associated with use of GEDmatch (β=-0.414, $p<0.05$). Interest in having raw data as a motivation for DTC testing was moderately associated with use of two tools: DNA.Land (β=0.241, $p<0.05$) and Interpretome (β=0.585, $p<0.05$). No other DTC testing motivations were associated with use of specific tools. Survey recruitment venue was strongly associated with tool use, as GEDmatch and DNA.Land users were more likely to have been recruited via Facebook while Promethease users were more likely to have been recruited from Reddit or the openSNP newsletter. DTC test(s) ordered were also linked to tool use (see also Figure 2.5), with the most significant associations between 23andMe and Promethease (β=0.641, $p<0.001$) and AncestryDNA and GEDmatch (β=0.987, $p<0.001$).

The large proportion of respondents using multiple third-party tools, including tools spanning the disparate categories of health, ancestry, and genealogy, led me to next examine combinations of tools used. I grouped respondents into those using only health-related tools (n=98 respondents); only non-health tools (n=263); and those using both types (n=458), which I refer to as the "crossover group" (see Table 2.2 for tool characterization). I present differences in DTC testing motivations, DTC test(s) ordered, and demographics between the three groups (health-only tool users, non-health only, and crossover group) in Tables 2.1 and 2.4. There was a linear trend in age, where non-health only tool users were oldest (mean age = 51.8), health only tool users were youngest (mean age = 39.4), and the crossover group was in between (mean age = 45.5). The health-only tool group had a significantly lower proportion of females (53% versus > 68% in the other two groups) and higher proportion of respondents

Table 2.3. Results from logistic regression analyses of tool use, separately for each tool with at least 40 reported users (see Table 2.2, column "Total users"). Each regression was run with a binary outcome (yes/no for tool use) and the following predictor variables: eight DTC testing motivations (each coded as 3=very important, 2=somewhat important, 1=not at all important); recruitment venue, where Facebook was the reference category; and DTC tests ordered (yes/no for each of 23andMe, AncestryDNA, and FamilyTreeDNA). Each column shows the β coefficients and standard errors (in parentheses) for the given predictor term (each row) when testing for use of the tool name given in the column. Bolded text and asterisks indicate significant p-values: ***p < 0.001, **p < 0.01, *p < 0.05. The sample size for each regression test is 845 respondents (the subset of 870 survey respondents who had downloaded raw data and had non-missing observations for all predictor variables).

		GEDmatch	**Promethease**	**DNA.Land**	**openSNP**	**Genetic Genie**	**Interpretome**	**Livewello**
DTC testing motivations	General curiosity	-0.125 (0.261)	0.255 (0.157)	-0.123 (0.155)	-0.068 (0.332)	-0.470 (0.347)	-0.077 (0.329)	0.354 (0.440)
	Ancestry	**.623*** (0.187)	-0.025 (0.143)	**.358** (0.135)	0.476 (0.274)	-0.129 (0.248)	0.344 (0.28)	-0.292 (0.275)
	Find relatives	**.509** (0.157)	-0.228 (0.118)	0.007 (0.111)	-0.070 (0.222)	-0.053 (0.221)	0.080 (0.232)	-0.113 (0.244)
	Risk for specific diseases	**-.414*** (0.177)	**.659*** (0.125)	-0.084 (0.118)	**.460*** (0.225)	**.933*** (0.271)	-0.059 (0.24)	**1.015*** (0.299)
	Limited family health history	-0.056 (0.155)	-0.191 (0.111)	0.050 (0.104)	-0.260 (0.198)	-0.106 (0.203)	-0.022 (0.210)	-0.183 (0.225)
	Other family members using	-0.067 (0.175)	-0.222 (0.118)	-0.186 (0.115)	0.032 (0.211)	-0.114 (0.228)	0.155 (0.215)	-0.211 (0.260)
	Participate in research	0.161 (0.160)	-0.029 (0.116)	0.214 (0.110)	0.314 (0.208)	0.080 (0.213)	-0.180 (0.218)	-0.041 (0.236)

	Raw genetic data file	0.055 (0.177)	0.065 (0.118)	**.241*** (0.114)	-0.086 (0.232)	0.280 (0.260)	**.585*** (0.264)	0.248 (0.290)
Recruitment Venue	Reddit	**-1.602***** (0.316)	**.512*** (0.225)	**-.786***** (0.210)	0.394 (0.398)	-0.121 (0.417)	0.520 (0.435)	0.145 (0.468)
	Twitter	**-3.282***** (0.513)	**-1.447***** (0.418)	**-1.451***** (0.404)	**1.596**** (0.538)	-0.454 (0.728)	1.159 (0.613)	-0.739 (1.108)
	openSNP	**-2.025***** (0.445)	**1.018*** (0.410)	**-1.334***** (0.345)	21.390 (921.613)	**1.006*** (0.491)	**1.481**** (0.508)	**1.620**** (0.516)
	Other	**-3.415***** (0.769)	-0.644 (0.628)	**-2.938**** (1.063)	**2.174**** (0.721)	0.767 (0.897)	1.486 (0.871)	-13.118 (671.629)
DTC tests ordered	23andMe	**.764*** (0.328)	**.641***** (0.177)	**.378*** (0.177)	**.871*** (0.393)	**1.144*** (0.513)	0.641 (0.406)	0.496 (0.449)
	AncestryDNA	**.987***** (0.295)	**.611**** (0.204)	0.137 (0.191)	0.179 (0.378)	-0.748 (0.406)	-0.243 (0.384)	0.662 (0.437)
	FamilyTreeDNA	**1.287**** (0.410)	0.193 (0.185)	**.401*** (0.179)	0.242 (0.371)	0.251 (0.411)	0.249 (0.382)	0.461 (0.402)

Figure 2.5. Tools used based on DTC test(s) taken, over 820 respondents who reported using at least one TPI tool. Darker blue shading on bars indicates tools that offer health-related information (see Table 2.2).

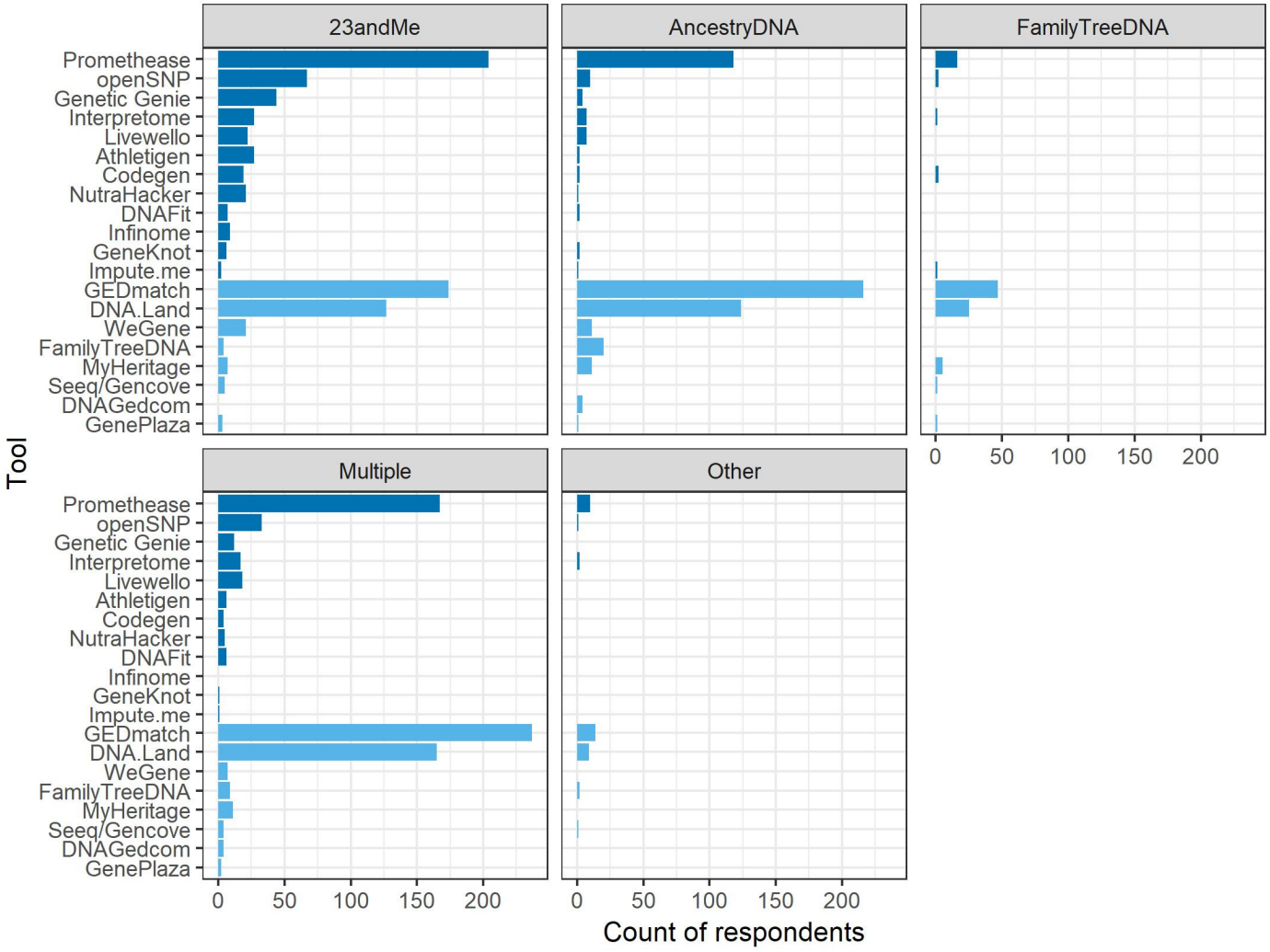


Table 2.4. Comparison of DTC tests ordered and DTC testing motivations, overall and grouped by type(s) of tools used.

Variable category	Variable	Overall	All tool users	Non-health only tools	Crossover	Health only tools	p-value[a]
	Number of respondents	1,137	820	263	458	98	
DTC tests ordered (%)	23andMe	62.4	61.7	40.7	68.1	87.8	<0.001
	AncestryDNA	53.9	59.8	73.0	62.0	14.3	<0.001
	FamilyTreeDNA	26.8	30.2	37.3	32.1	3.1	<0.001
Mean rating of DTC testing motivations[b] (SD)	General curiosity	2.64 (0.55)	2.64 (0.56)	2.47 (0.65)	2.69 (0.5)	2.82 (0.41)	<0.001
	Ancestry	2.6 (0.59)	2.61 (0.59)	2.65 (0.57)	2.65 (0.56)	2.28 (0.69)	<0.001
	Find relatives	2.21 (0.83)	2.27 (0.81)	2.52 (0.68)	2.3 (0.79)	1.5 (0.74)	<0.001
	Risk for specific diseases	2.02 (0.78)	2.01 (0.78)	1.63 (0.75)	2.13 (0.74)	2.46 (0.64)	<0.001
	Limited family health history	1.73 (0.78)	1.73 (0.78)	1.7 (0.8)	1.76 (0.78)	1.66 (0.77)	0.406
	Other family members are using	1.42 (0.68)	1.41 (0.67)	1.44 (0.68)	1.42 (0.68)	1.28 (0.61)	0.108
	Participate in research	2 (0.8)	1.99 (0.8)	1.87 (0.8)	2.04 (0.8)	2.06 (0.8)	0.018
	Raw genetic data file	2.32 (0.77)	2.37 (0.75)	2.22 (0.79)	2.41 (0.74)	2.54 (0.61)	<0.001

[a]Comparing non-health only tool users, crossover tool users, and health-only tool users. P-values are from either Chi-square or Fisher exact tests for categorical values and from ANOVA for continuous variables, comparing three groups (non-health only, both, health-only).

[b]For DTC testing motivations, 3=very important, 2=somewhat important, 1=not at all important

SD = standard deviation

working in genetic research or medicine (13% versus <= 3% in the other two groups). DTC test(s) ordered were significantly different between the three groups, with the proportion of 23andMe customers increasing from the non-health group (40.7%) to crossover group (68.1%) to health-only group (87.8%) and a reverse pattern for both AncestryDNA and FamilyTreeDNA (proportion decreasing from non-health to crossover to health-only; see Table 2.4). Notable associations between DTC testing motivations and user group included increasing importance of general curiosity about genetics from non-health to crossover to health-only. Interest in having raw data was highest among the health-only tool group and lowest in the non-health only, suggesting that those who exclusively used health-related TPI tools were more highly motivated by raw data access when pursuing DTC testing.

Interviews with crossover tool users

In follow-up interviews with respondents in the crossover group, I observed tool crossover in both directions: three initially used health-related tools before trying non-health tools, and four initially used non-health tools before trying health-related tools, illustrated by quotes in Table 2.5. In contrast to those who began with an interest in one domain then moved to another, for three interviewees who were either adopted or had an adopted parent, interest in health and genealogy were inextricably bound together in their search to simultaneously learn about their biological family and potential implications for their own health risks.

The primary phenomena responsible for tool crossover were social networking, general curiosity, and initial lack of interesting findings. Facebook and Reddit were the primary social networks in which participants learned about multiple tools, including those seemingly outside the scope of the given Facebook group or sub-Reddit. Once participants learned about additional tools, they tried them often out of curiosity or general hunger to learn more, in particular to go beyond the information provided in DTC company reports. An initial lack of interesting findings in one domain also pushed some participants to seek out tools in another area.

Table 2.5. Interview quotes related to the theme of crossover/use of tools across the domains of health, ancestry, and genealogy. Participant ID given in parentheses following each quote.

Initial use of health-related tools:
I was interested in finding out exactly what my DNA meant, not just what 23andMe wanted to tell me, but maybe other information I could glean from it…I think I used Promethease first…from what I could tell, it was the most information...[On additionally using GEDmatch] I may have just Googled "things to do with raw DNA". I just wanted something different from Promethease. Specifically, I wanted to see if I could find matches other than what 23andMe had found for me. (574)
I got quite frustrated how boring I am in terms of my ancestry [from DTC reports], there's hardly any variation...I think that's why I decided to concentrate more on the health side of things rather than the rather dull ancestry part, because I was hoping to find something quite exciting and something I didn't know about before, and the health side provided that — but the ancestry didn't…[On additionally using GEDmatch and DNA.Land] On a lot of these forum posts, they tend to list the third party websites along with their cost. GEDmatch and DNA.Land come up frequently in these lists on the posts. (58)
Initial use of non-health related tools:
I was primarily focusing on genealogy at that point [when first using TPI tools]…I may have found Promethease mentioned online or in an article I read…I just said, “Oh, that's cool.” So I did that…It's just general interest, I just wanted to see if there was anything to the health thing, and I don't carry anything specific…I didn't think I did, but it's good to know. But the genealogy thing is what I've been focusing on mostly, because the health is all like, “Ok, I know. I could get heart disease.” I don't have any “bad genes,” as they say — the high correlation ones. I don't really have any of those. (798)
I wasn't doing it [using TPI tools] for health at all and just when I saw the Promethease and I thought, "Well for five dollars, you know, we'll see what it says." (559)
When I did download [raw data] for the first time, it was specifically to upload to GEDMatch…After that, I explored what else I could do and found out that I could get more matches by doing free uploads to other sites. I uploaded to DNA.land, Geni, MyHeritage and FamilyTreeDNA. Through membership of a genealogy Facebook group, I found out about Promethease and did that out of curiosity. (664)
Inextricably linked (e.g., for adoptees)
I'm adopted, and I know a limited amount about my biological mother. I wanted to see if I could fish around and find out what was going on the other side, find anybody that I was connected to. I was doing all kinds of testing…partly I was trying to take control of whatever health information I could get, but then also fishing around for family connections. I was doing some of each. (577)
Partially it was ancestry, partially it was finding my bio family, partially it was finding out what [family history] boxes can I check now when I go to the doctor's office. It's a little bit of everything which all comes together for a big ball of happy…It’s not any one single reason. (226)

Discussion

In this sample of DTC customers, I found high rates of raw data download and usage of TPI tools. Given some of my recruitment venues, this volume of TPI tool use may be expected; however, the scale and scope were remarkable. Specifically, respondents reported using on average three different TPI tools, often spanning a range of health, ancestry, and genealogy. Users of different tool categories (health, non-health, and both) differed in their demographics, motivations for DTC testing, and DTC tests taken. In follow-up interviews with a subset of crossover users (i.e., those using both health and non-health tools), I observed individuals often migrated to using tools outside their original scope of interest due to peer-to-peer sharing on social networks, general curiosity, and/or initial lack of interesting results. Below I discuss implications of these findings for the medical genetics community and health care systems more broadly.

As with DTC testing, one concern with TPI tool usage is downstream overutilization of scarce health care resources, or "raiding of the medical commons" (McGuire & Burke, 2008). Indeed, of the few accounts of TPI tool usage to date, several have focused on interactions with the health care system (Allen et al., 2018; Moscarello et al., 2018; Tandy-Connor et al., 2018). These prior studies rightly illustrate the potentially alarming outcomes of patients' misunderstandings of TPI reports; however, they do not indicate how often these scenarios result from "garden variety" TPI tool usage. In the current study, I observed a relatively low reported rate of sharing TPI results with HCPs (15%). This rate was lower than the 30% (of 321 surveyed) previously reported by Wang et al. (2018), which may be due to my participants responding based on a specific tool rather than across all tools used. Indeed, when limiting to respondents who answered based on Promethease, my rate of HCP sharing was comparable (29%). Likely of concern to genetics professionals is that among respondents who shared with HCPs, the majority (79% of 116) did so with general practitioners or non-genetics specialists, rather than with medical geneticists or GCs. This observation reinforces the need for increased genetics training among

primary care physicians (Baars, Henneman, & Ten Kate, 2005; Burke, 2004), perhaps even more intensely given that TPI reports are typically longer and harder to digest compared to DTC company reports (Allen et al., 2018; Badalato et al., 2017; Nelson & Fullerton, 2018, see also chapter 1).

Regardless of whether they brought TPI reports to providers, respondents were frequently engaging with health information via TPI (i.e., 68% of tool users used health-related tools; see also Table 2.2). This was true even for respondents who were initially intent on finding relatives and receiving ancestry percentages. Due to the flow of information on social media platforms such as Facebook and Reddit, respondents who started off using tools in one domain often switched or "crossed over" to using tools in another. This has implications for those whose TPI reports eventually do prompt them to interact with the health care system. For example, those initially interested in genealogy who later use health tools may be more likely to overestimate the reliability and comprehensiveness of the health information. There is relatively little uncertainty in identifying close relatives from genotyping array information; as one interviewee said about genetic genealogy, "DNA doesn't lie." This is in stark contrast to disease prediction based on similar data, which is far more probabilistic and uncertain. Furthermore, the raw data is incomplete given that it is based on array genotyping rather than genome sequencing, and may even be incorrect (Tandy-Connor et al., 2018). The opposite effect is also possible: those involved in both paper trail and genetic genealogy may realize that genetics alone does not provide complete information when researching family history and so may be better equipped to understand limitations of health-related genetic information. Providers who better understand the course patients have taken to leverage their raw data via TPI may be better equipped to calibrate and manage patient expectations and understanding.

Another important finding is that approximately 40% of tool users agreed they had received health information, including about disease risk. This contrasts with my prior study of tool developers in which they characterized tools' direct linking to scientific publications or variant annotation databases as

merely “bridging to the literature” and hence stopping short of actual *interpretation* (Nelson & Fullerton, 2018). However, my survey data suggests users regard TPI reports as providing personally relevant health information. At the same time, developers’ claims that “bridging” may increase understanding of genetic risk (Badalato et al., 2017; Nelson & Fullerton, 2018) were supported by my survey results: the majority of respondents agreed that using TPI tools increased their understanding of genetics in general (76%) and in particular how DTC companies interpret genetic data (67%).

To my knowledge, this is the largest study to date of raw data and TPI tool usage. However, my recruitment of a convenience sample via social media limits my ability to generalize findings to DTC customers more broadly. Specifically, my respondents are likely highly motivated individuals who were active in these online forums and thus may overestimate the degree of data download and tool usage. The relatively small number of non-downloaders may not have provided enough power to detect differences with downloaders. However, I contend limited generalizability is mitigated in part by my collection of qualitative data through open text survey responses and follow-up interviews, which generated deeper understanding of users’ motivations and experiences. Convenience sampling also allowed a rapid collection of a large number of respondents already engaged in the topics of interest, which seems appropriate for gaining preliminary insight into a relatively understudied area. The length of the survey may have contributed to the 24% non-completion rate and therefore potential survey item response bias, though compared to prior surveys (Wang et al., 2018), I collected more extensive and granular information about specific tool usage. Some incongruities between information reportedly received and the actual offerings of tools suggests that respondents may not have limited responses to the selected tool as directed; however, these incongruities were not widespread.

I have focused on the consumer genomics context as it is currently the most common way to access raw data. However, this work can help predict how broadening routes of access may unfold. Since 2014, the HIPAA direct access right has allowed individuals to access the contents of their

designated record sets (U.S. DHHS, 2014), which for clinical sequencing laboratories would likely include uninterpreted sequence data (U.S. DHHS, 2016). Laboratories are not required to provide additional explanation or interpretation, which may lead recipients to seek out TPI. Indeed, many TPI tools accept the Variant Call Format (VCF) file type common to genome and exome sequencing (Nelson & Fullerton, 2018). Another potential route to raw data access is through participation in genetic research. Social and policy norms are changing to support and even encourage researchers to allow participants access to their individual-level data and research results (Karow, 2018; Lunshof et al., 2014; NASEM, 2018; Nelson, 2016), including in the "All of Us" program (Karow, 2018). Future research should evaluate how individuals' interactions with their raw data potentially differ across these contexts.

In summary, moving forward individuals will have increasing routes to access their raw genetic data and leverage it in an expanding menu of largely unregulated TPI services. These activities raise a set of concerns related to but distinct from DTC genetic testing and thus merit further investigation to more fully understand potential harms and benefits. Rather than taking sides in a potential ensuing "culture war" about raw data (Evans & Green, 2009), the genetics community has an opportunity to proactively engage with users, understand the complexity of their motivations for pursing third-party analysis, and ultimately educate them about potential limitations.

CHAPTER 3: INFORMING POLICYMAKING CONCERNING THIRD-PARTY INTERPRETATION OF CONSUMER GENOMICS DATA: SCIENTIFIC AND OTHER CONSIDERATIONS FOR POLICYMAKERS

Abstract

Potential risks to consumers from false positives returned from third-party interpretation (TPI) of direct-to-consumer genetic testing (DTC-GT) data make the area ripe for policymaking. However, policymakers will need a nuanced understanding of TPI and its relationship to DTC-GT before considering appropriate responses. In this chapter, I begin with a description of the distributed, supply chain nature of raw data provision and TPI, including its actors and their roles: genotyping array manufacturers; DTC-GT companies, including the genotyping laboratories to which they contract out; TPI tools; and the variant annotation databases on which many TPI tools and array manufacturers rely. Next, I map some aspects of the regulatory landscape that should be informed by a fuller understanding of that supply chain structure and underlying scientific and technical aspects of each component. I focus on U.S. federal health regulations administered by the Food and Drug Administration and the Centers for Medicare and Medicaid Services. Ultimately, the regulatory landscape is complicated by potential disconnects between the emphases of DTC-GT companies and TPI tools (e.g., health versus ancestry); the dearth of empirical evidence regarding harms and benefits to DTC-GT customers; and the evolving landscape of genetic testing regulation more broadly. I conclude that any policymaking in this area will need to recognize the distinctions between different components in the supply chain system, including separation between production of raw data and its interpretation, and account for unique qualities of TPI tools, such as the volume and heterogeneity of information provided, the dynamic nature of TPI reports that link to evolving databases of scientific literature and human variation, and the variety of business models represented.

Introduction

> *The fault doesn't lie with the third-party analysis service…Those companies simply analyze the raw data received from consumer testing companies. The errors were in the raw data.*
>
> - Stephany Tandy-Connor, genetic counselor, quoted in Saey (2018)

Direct-to-consumer genetic testing (DTC-GT) enables individuals to access personal genetic information about health/wellness, ancestry, and relatedness to other customers. Over 12 million individuals[2] have reportedly pursued DTC-GT, and the industry shows no signs of slowing (ISOGG, 2018; Regalado, 2018). In addition to providing interpreted reports, most DTC-GT companies also allow customers to download their "raw" or uninterpreted genetic data file (GDF). The GDF is essentially a long text file listing the customer's genotypes (A's, C's, G's and T's) at the hundreds of thousands of DNA sites tested by the company. Both portable and multi-functional, these GDFs can be used in a growing list of independent, online third-party interpretation (TPI) tools (Badalato et al., 2017; Nelson & Fullerton, 2018; Spector-Bagdady & Pike, 2014; Wang et al., 2018). Similarly to DTC-GT companies, TPI tools can be categorized according to their focus on one or more types of interpretation: health/wellness, ancestry, and/or genealogy. This bifurcation between data provider and data interpreter leads to the situation where a GDF from a DTC-GT company with one focus (e.g., ancestry) can be used in a TPI tool with a wholly different focus (e.g., health). This type of flexibility is inherent to

[2] Regalado (2018) in February 2018 estimates over 12 million customers. The International Society of Genetic Genealogy (ISOGG 2018) Wiki maintains updated tallies by company and, as of an October 13, 2018 update, indicates upwards of 18 million customers. The more conservative Regalado figure is cited because it is not entirely clear how ISOGG updates its counts. Furthermore, the survey of DTC-GT customers presented in chapter 2 revealed that people order tests from more than one company, such that there might be double counting (i.e., the same individual is counted multiple times across different DTC-GT companies).

the genome, which carries information about both distant and recent relatedness (i.e., ancestry and family relationships) as well as predispositions to certain health-related conditions and diseases.

Several recent media anecdotes[3] demonstrate the possible harms to consumers when TPI of raw DTC-GT data yields a false positive result. For example, as reported by the *Huffington Post* in April (Almendrala, 2018), a 23andMe customer downloaded her GDF and uploaded it to the TPI tool Promethease. Her Promethease report indicated she had a risk variant in the *MSH2* gene predisposing her to Lynch syndrome (rs63751426, C > T), a hereditary cancer predisposition syndrome. Follow-up clinical testing determined this to be a false positive. There are several troubling aspects of the anecdote. First, this 23andMe customer and her partner both experienced psychological distress and anxiety after receiving the Promethease report. Second, the false positive triggered unnecessary further testing that consumed scarce health resources — in this case, directly from the customer's pocket (she paid for her follow-up test and was not reimbursed by insurance). Lastly, she knew how to seek follow-up care and treatment in part because she works in a large cancer research center. A less well-positioned and well-informed person may not have had the same recourse to follow-up on the troubling result and therefore may never have obtained corrected information.

Pinpointing responsibility for this potentially harmful incident requires discerning the specific source of the error and placing it in the broader context of raw data access and TPI. The conflation among different potential sources of error is apparent in the media coverage, and also in responses observed from the professional genetics community. Contrary to the article's statement "Promethease

[3] This section references traditional and social media anecdotes rather than published, peer-reviewed literature in part because there are few studies of TPI and its impact on both users and the public more broadly. Instead, TPI appears more prominently in recent media articles and on social media, and as such these are the platforms where the general public and journalists are being exposed to these issues. Furthermore, social media platforms such as Facebook, Twitter, and Reddit are where information about TPI tools often circulates among tool users (e.g., see chapter 2). Therefore, these alternative sources of information and examples are valuable in providing insight into this novel and rapidly evolving area.

had turned up a false positive result," the error was in fact the raw genotype in the 23andMe GDF: the variant annotation database ClinVar reports rs63751426 to be pathogenic as determined by expert panel review (https://www.ncbi.nlm.nih.gov/clinvar/35435018/). Therefore it is not surprising Promethease returned a pathogenic result, as the tool uses automated processes to incorporate variant information from ClinVar and other scientific resources (e.g., PubMed) to populate its reports (Nelson & Fullerton, 2018). The 23andMe assay at this variant location, on the other hand, showed an unusually high missing call rate (~13%) when analyzed by a developer of the open genotype database openSNP (gedankenstuecke, 2018), which contains GDFs primarily uploaded by 23andMe customers (Haeusermann et al., 2017). Such high missing call rates often indicate a problem with genotyping quality (Laurie et al., 2010). Similar stories of false positives have appeared in the *New York Times* (Hercher, 2018; Kolata, 2018a), all ultimately tracing back to errors in the raw genotypes included as part of the DTC-GT GDF.

Members of the professional genetics community may also fail to understand other fundamental aspects of TPI, including how raw data from a DTC-GT company with one focus (e.g., ancestry) can be used in TPI tools with an entirely different focus (e.g., health/wellness). This misunderstanding is illustrated by reactions to a Tweet from a genetic counselor describing a similar anecdote about false positives. The genetic counselor saw a patient who had received a positive *BRCA* result after downloading her GDF from AncestryDNA and running it through Promethease (Karen_GC_Cincin, 2018). As with the *MSH2* incident above, follow-up clinical testing found it to be a false positive due to an error in the raw genotype rather than the TPI. A Stanford geneticist replied to the Tweet: "Wait - @ancestry doesn't report disease alleles period - it must have come from a different company. @ancestry reports - wait for it - ancestry!" (gsherloc, 2018). His comment reflects an incredulity that many in the genetics community and general public may share: that health information, and in particular *BRCA* variants, could be extracted from an AncestryDNA test. This response illustrates a

failure to recognize that genotyping arrays used by DTC-GT companies contain much more genetic information than is directly incorporated into the companies' reports. In fact, the base array historically used by AncestryDNA contains ~60 SNPs in *BRCA1* and *BRCA2*, 40% of which are annotated as exonic missense and therefore of potential clinical relevance (blueyedgenes, 2018)[4].

As exemplified by the anecdotes above, false positive results from TPI may produce several negative outcomes, including harms to consumers who experience emotional distress and financial hardship in seeking out further information, burdens on health care providers (HCPs) who may be tasked with providing guidance to patients in areas with which they are unfamiliar, and strains on health care systems bearing the costs of follow-up testing. These problems are of potential interest to policymakers, including regulators. Here I consider protecting consumers[5] from false positives as the primary policy problem, recognizing that false positives can have ripple out effects to providers and health care systems as noted above.

Any policymaking in the novel and increasingly popular area of DTC-GT raw data usage and TPI will require a nuanced understanding of the underlying science and technologies before appropriate responses can be considered. There are several inherent complexities associated with TPI that need to be appreciated when evaluating the relevance and applicability of existing oversight mechanisms and whether new policies need to be developed, as discussed further in the sections on federal health

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[4] This citation is for my contribution to the Twitter thread. In that contribution, I described how I determined the number of *BRCA1/2* genes on the OmniExpress array by downloading the array manifest, "HumanOmniExpress-24v1-1_A.annotated.txt," from the Illumina website (https://support.illumina.com/array/array_kits/humanomniexpress-24-beadchip-kit/downloads.html). I then searched for variants mapped to *BRCA1* or *BRCA2* in Illumina's annotation, which yielded 65 variants, and further filtered to those variants annotated as exonic missense (a crude proxy for potential clinical relevance) in that same annotation. AncestryDNA used the OmniExpress array until May 2016, as discussed in the "SNP array manufacturers" section.

[5] Notably, this stakeholder group can be named differently according to location in the supply chain system at any given time: as DTC-GT customers they are *consumers* of a commercial product; when using DTC-GT raw data in TPI tools, they are tool *users* (rather than "consumers," given that many tools are non-commercial); and when potentially bringing TPI reports to HCPs, they are *patients*.

regulations. These complexities include the distributed, supply chain nature of raw data provision and TPI, where errors can occur at different stages (e.g., in the raw data and/or the TPI report); the heterogeneity of TPI tools; potential disconnects between the emphases of DTC-GT companies and TPI tools (e.g., health versus ancestry); a dearth of empirical evidence regarding potential harms and benefits to TPI tool users; and the evolving landscape of genetic testing regulation more broadly. The potential misunderstanding of genetics professionals in the anecdotes above suggest that policymakers have an even steeper hill to climb in gaining the necessary background knowledge to understand those complexities.

Some analogies exist that policymakers could consider, though none of them cleanly fit TPI. For example, patient and consumer use of GDFs from DTC-GT companies in TPI systems elicits many of the same concerns and challenges raised about the provision of interpreted reports from DTC-GT companies, including risk of consumer misunderstanding and psychological distress (Bloss et al., 2011; Dohany, Gustafson, Ducaine, & Zakalik, 2012) and unnecessary consumption of limited health care resources (McGuire & Burke, 2008). However, the distinctions between "traditional" DTC-GT and use of DTC-GT GDFs in TPI tools may exacerbate these concerns and challenges. First, there may be disconnects between the focus of the DTC-GT company from which a GDF is downloaded and the potential orientations of the myriad TPI tools a consumer might use, amounting to what could be considered "off label" use of DNA with subsequent "off target" effects. Second, to the extent that regulation of DTC-GT testing has been a moving target (Annas & Elias, 2014; Caulfield & McGuire, 2012; Palmer, 2012), the regulatory landscape of TPI is unclear at best and nonexistent at worst, as discussed further in the sections on federal health regulation.

In addition to appreciating the scientific and technical aspects of TPI that set it apart from potentially analogous areas, policymakers will also need to balance a complex set of ethical concerns when considering appropriate responses. These ethical concerns include respect for individual

autonomy, just allocation of finite health care resources, and minimization of harms in the least restrictive way possible (Childress et al., 2002). For example, regulation that limits or otherwise constrains individuals' access to their genetic data and its use in TPI systems could easily diminish their autonomy and alienate the individuals such regulation aims to protect. Indeed, debates about regulation of DTC-GT often involve a tension between respect for individual autonomy and consumer protection (Vayena, 2015); a similar dynamic exists in considering regulation of DTC-GT raw data and TPI. Recent years have seen a growing discourse of patient empowerment, democratization of the genome information (Lee, 2013; McGowan et al., 2010), and a "participatory turn" in biomedical research (Prainsack, 2011), apparent in the very title of the recently launched Precision Medicine Initiative research cohort known as "All of Us" (NIH, 2018). Policies that are out of touch with this ethos by enacting a premature paternalism (e.g., denying people their personal data or limiting access to TPI) may drive a wedge between the biomedical research community and the participants with whom they wish to partner. The proverbial cat is already of out of the bag: the consumer/user/patient has become a steward of her genetic data in a heterogeneous world of online interpretation services.

Furthermore, a policy discussion solely focused on consumer protection against the potential harms of false positive results overlooks numerous potential benefits to the consumer/user/patient stakeholder group. Through DTC-GT raw data access and TPI, an individual may receive a true positive result that motivates them, and potentially their family members, to seek medical attention that could ultimately divert or delay the onset of disease. Genealogy and ancestry information obtained through TPI may benefit individuals by identifying lost family members, which can foster a sense of connection and provide missing family health history (e.g., for adoptees). Using TPI tools whether for health, ancestry, or genealogy may simply provide an enjoyable pastime or allow various forms of "data play" (Furbo, 2016).

To help inform policymakers, here I present a scientist's perspective on raw data and TPI tools. First, I describe scientific and technical details of each component in this distributed, supply chain system: genotyping array manufacturers; DTC-GT companies, including the genotyping laboratories to which they may contract out; TPI tools; and the variant annotation databases on which many TPI tools and array manufacturers rely. Next, I highlight areas of regulation that should be informed by a fuller understanding of these scientific and technical aspects, focusing on U.S federal health-related regulations administered by the Food and Drug Administration (FDA) and Centers for Medicare and Medicaid Services (CMS). This discussion of existing or potential regulatory responses is not meant to be comprehensive but rather to illustrate for policymakers how a robust scientific understanding of TPI should inform policy deliberations. The timeliness of these considerations cannot be overestimated. The market for DTC-GT, in particular for ancestry and genealogy testing, continues to grow (Regalado, 2018), alongside an increasing number of TPI tools (Nelson & Fullerton, 2018). The scope of the issue will also expand as DTC-GT companies transition from array-based genotyping to genome sequencing (Niemiec & Howard, 2016), which could provide 3,000 times as many raw genotypes (i.e., 3 billion from a whole genome sequence versus 1 million from an array) and would include more rare and likely pathogenic variants.

The components

SNP array manufacturers

While DTC exome and genome sequencing services are starting to become available (Helix, 2018; Niemiec & Howard, 2016), most existing DTC-GT companies use commercially available SNP (Single Nucleotide Polymorphism) array genotyping technology or "SNP chips" to measure customer genetic variation. To maximize market share, array manufacturers design genotyping products to attract a diverse set of researchers, institutions, and commercial entities, resulting in arrays with both health-

and ancestry-related content. The DTC-GT companies FamilyTreeDNA and MyHeritage both use the Illumina OmniExpress array (ISOGG, 2018). AncestryDNA used the OmniExpress until May 2016, when it switched to a custom Illumina chip that includes additional medically-relevant content (Estes, 2017), perhaps related to the company's expressed interest in moving into health-related testing (Duhaime-Ross, 2015). While 23andMe has used several different arrays since 2007, including the OmniExpress, since November 2017 they have used a customized version of Illumina's newer Global Screening Array (GSA) (23andMe, 2017b; Estes, 2017). Both the OmniExpress and GSA have between 600,000 and 800,000 SNPs and are strategically designed to cover different types of genetic variation (Illumina, 2016, 2017).

A substantial proportion of array content (e.g., 89% of GSA) is dedicated to a genome-wide scaffold of relatively common variants known as "tagging" variants, which have utility for both non-commercial researchers and DTC-GT companies. Tag SNPs are selected to represent longer stretches of co-inherited (but not directly assayed) variation along the chromosome (haplotypes) and are useful in genome-wide association studies (GWAS) and imputation. In GWAS, testing for associations between a phenotype and genotypes at tag SNPs can help point to neighboring causal variants (Wang, Barratt, Clayton, & Todd, 2005). Similarly, in genome-wide imputation, a sparse scaffold of tag SNPs enables comparison of haplotypes between a study sample and a more densely genotyped or sequenced reference sample to impute (or infer) missing genotypes for the study sample (Marchini & Howie, 2010). Both properties, enabling GWAS and imputation, are highly valuable in the genetic research and DTC-GT contexts. The genome-wide scaffold of common variation is also valuable for both estimating genome-wide and local (along a chromosome) ancestry and identifying and characterizing genetic relatedness (i.e., finding relatives) (Laurie et al., 2010) — also goals of many DTC -GT companies.

In addition to the genome-wide scaffold content just described, these arrays also dedicate real estate to either known or candidate disease-related loci. Product information for the OmniExpress

describes strategic selection of SNP content to "drive the discovery of novel associations with traits and diseases" (Illumina, 2016). For example, GSA product information describes the selection of SNPs to enable clinical research, noting that >55,000 markers were selected based on records from the variant annotation databases ClinVar, Pharmacogenomics Knowledge Base, the National Human Genome Research Institute (NHGRI) GWAS Catalog, and putative functional variants from the Exome Aggregation Consortium. 23andMe has customized the GSA array with an additional ~50,000 SNPs, described as optimizing the ancestry analysis and "to help standardize the platform for genetic research" (23andMe, 2017b). It is also possible some of the custom content was added to enable specific health reports, though not explicitly stated in the company announcement.

DTC-GT companies

Here I focus on DTC-GT companies as the providers of raw data to customers, rather than as providers of various interpreted reports (e.g., reports on health/wellness or ancestry). The major DTC-GT companies allow customers to download their GDF, including AncestryDNA, 23andMe, FamilyTreeDNA, and MyHeritage (ISOGG, 2018). Notably, some DTC-GT companies also allow upload of GDFs from other companies, effectively placing them in the dual role of both raw data provider and third-party interpreter (Larkin, 2017; Nelson & Fullerton, 2018). DTC-GT companies endorse the customer's right to her personal data while simultaneously proffering disclaimers that, in general, raw data has not been validated at the level of individual variants and should not be used for anything beyond informational, educational, or research purposes (i.e., should not be used in diagnostic or other medical decision-making). Companies walk a fine line between advertising the GDF as a benefit of the service on the one hand while on the other hand cautioning against how GDFs are used, as evidenced by the language on company websites. For instance, a 23andMe Customer Care article notes "raw data provided by 23andMe has undergone a general quality review however only a subset of markers have

been individually validated for accuracy" and that raw data is "suitable only for informational use and not for medical, diagnostic or other use" (23andMe, 2017a).

The balancing act between advertising GDF access as a benefit while noting its limitations is also apparent in companies' responses to user questions in a Reddit "Ask Me Anything" (AMA) forum[6] on personal genomics held in April 2018 (Personal Genetics Reps, 2018). The AMA was part of a series organized by the NHGRI in celebration of DNA Day, with the broad goal to "share our genomics expertise with the public through online question and answer sessions" (NHGRI, 2018). The AMA was attended by representatives from 23andMe, AncestryDNA, FamilyTreeDNA, National Genographic Project, and Helix as well as the clinical sequencing company Color Genomics. Compared to the somewhat constrained and careful language on company websites, in the AMA representatives were in a position to more directly address users' concerns and the critiques of other companies. While an unconventional source, in an area moving this quickly, online spaces such as Reddit can provide valuable insight into DTC-GT companies' positions and how they respond to their customers and competitors. Next, I briefly summarize relevant exchanges from the AMA to highlight companies' viewpoints on raw data quality, including the ability for array genotyping to accurately measure rare variation[7]; limiting use of raw data to information and education only; a customer's right to access her raw data; and limitations of TPI.

One Reddit user asked whether DTC-GT companies should be held responsible for genotyping errors, citing a recent publication indicating a 40% error rate in DTC-GT testing (Tandy-Connor et al., 2018). Spokespersons from 23andMe and AncestryDNA gave very similar responses: that raw data has

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[6] A Reddit "Ask Me Anything" (AMA) is an online forum where individuals of interest (e.g., celebrities, scientists, or experts on various topics) can respond to questions posed by Reddit users. While the AMA occurs on a given day and time, the questions and answers are preserved in the online record of the AMA. References and quotations in this section are primarily to the personal genomics AMA.

[7] While company representatives did not define "rare" in the AMA, rare variants are typically defined as those with minor allele frequency < 1% (e.g., see https://www.nature.com/subjects/rare-variants).

only undergone a “general quality review” and that genotypes at specific variant locations have not been “individually validated.” Notably, the 23andMe representative tried to distance the company from the Tandy-Connor et al. study by saying it was not based on the information 23andMe reports to customers and instead “looked at how other third parties interpreted raw data from a variety of consumer genetic companies” (Personal Genetics Reps, 2018, sec. “Smash_Meowth" answered by "Dave from 23andMe”). This is slightly misleading. While it is true that Tandy-Connor et al. (2018) reported instances of variant misclassification, including by TPI tools, the 40% false positive rate indeed refers to variants from DTC-GT raw data that were not observed in follow-up, confirmatory sequencing. On the other hand, the 23andMe representative was correct in that the Tandy-Connor study does not indicate a 40% false positive rate for DTC-GT raw genotypes in general, as the study focused on a subset of variants referred for clinical follow-up. In responding to this same user question, FamilyTreeDNA gave the shortest answer, noting simply: “Our DTC tests do not include results for medically actionable SNPs for this reason” (Personal Genetics Reps, 2018, sec. “Smash_Meowth" answered by "Connie from FamilyTreeDNA”). However, this assertion is questionable given the variety of content on the OmniExpress chip, as described above.

In response to a similar question from another Reddit user referencing the same Tandy-Connor et al. study, representatives from sequencing companies Color Genomics and Helix asserted that SNP arrays are less accurate at genotyping rare variation compared to sequencing. A 23andMe scientist rebutted that accuracy is not so directly tied to platform and that array genotyping can be fine-tuned to achieve comparable accuracy to sequencing for rare variants. She noted that at 23andMe they “specifically validate each genetic variant that we interpret and use in our genetic health reports, both from an analytical accuracy perspective and from a clinical interpretation perspective,” including for rare variants. However, she again highlighted how interpreted variants are “different from the raw uninterpreted genotyping data, which has not been validated and should not be used for medical

purposes” (Personal Genetics Reps, 2018, sec. “Worfs_Wharf" answered by "Shirley from 23andMe”). The 23andMe representative does not directly address the possibility that rare variants on the microarray not used in interpreted reports could indeed have higher error rates than one might expect from sequencing. Nevertheless, it is not surprising that spokespersons took positions consistent with the platform used by their respective companies. Both Helix and 23andMe touted CLIA (Clinical Laboratory Improvement Amendments of 1988) and CAP (College of American Pathology) accreditation of their genotyping facilities in the AMA, yet it is unclear what these accreditations would guarantee with respect to quality control of individual variants, as discussed further below in the section on laboratory certifications.

Linked to these caveats about raw data quality are DTC-GT companies’ disclaimers that use of raw data is limited to educational, informational, and research purposes only and should not be used for diagnostic or other medical decision making. These statements are made both on company websites (23andMe, 2018b; AncestryDNA, 2018b) and in the Reddit AMA. For example, a 23andMe representative in the AMA stated, “raw data is only suitable for research, educational, and informational use and not for medical, diagnostic or other use” (Personal Genetics Reps, 2018, sec. “Smash_Meowth" answered by "Dave from 23andMe”). This cautionary language is almost identical to disclaimers on the 23andMe website, which additionally warn customers to “[c]onsult with a healthcare professional before making any major lifestyle changes” (23andMe, 2017a). AncestryDNA is not as explicit about raw data availability on its website compared to 23andMe and therefore such disclaimers are not as readily discoverable by AncestryDNA customers. However, in the AMA an AncestryDNA representative cautioned users to “keep in mind that these results are not intended for diagnostic purposes. The SNPs within the raw DNA data have not been individually validated for diagnostic, medical or clinical use” (Personal Genetics Reps, 2018, sec. “Worfs_Wharf" answered by "This is Barry from Ancestry”).

While DTC-GT companies tell these cautionary tales, they also sing a celebratory song about customers' rights to access their own data. In fact, in the AMA, 23andMe ended their response to questions about data quality with this overture: "We believe that your genetic data is yours, and stand behind our decision to provide users with access to all of their data, including their raw uninterpreted data." Notably, 23andMe also advertises raw data availability as a key feature of their product (23andMe, 2018b). One of AncestryDNA's AMA responses also highlights a similar position: "Ancestry customers own their genetic data and are welcome to download their raw DNA data for genealogical research and general information" (Personal Genetics Reps, 2018, sec. "Worfs_Wharf" answered by "This is Barry from Ancestry"). While the exact meanings of "own" and "yours" are not provided, companies appear to want to promote customer autonomy and to vocalize their support of access to personal genetic data — indeed that direct access is a general premise on which the DTC-GT industry is built. More shrewdly, companies also likely recognize customer demand for raw data and the backlash that would arise from restricting access. The uproar caused by the FDA taking away 23andMe health reports is evidence enough of repercussions from restricting access, especially for previously available information (Regalado, 2014).

DTC-GT companies' willingness to talk about raw data access contrasts with some degree of reluctance in acknowledging TPI services. In a customer support article, AncestryDNA encourages customers to do their due diligence before uploading to third-party sites, including to check for existence of a privacy policy, Institutional Review Board oversight, an option to delete data, and security and encryption of the website (AncestryDNA, 2018b). Notably, 23andMe's main customer-facing information does not address TPI tools so directly, perhaps for fear that it would be seen as a tacit endorsement or nudge for customers to pursue TPI. When asked directly their opinion on TPI tools such as Promethease in the AMA, a 23andMe representative stated, "it is important to understand that 23andMe is not affiliated with any third-party interpretation services and does not endorse, sponsor, or

recommend any third-party interpretation services" (Personal Genetics Reps, 2018, sec. "genomegal" answered by "Greg from 23andMe"). They added caveats similar to the ones on AncestryDNA's website, namely to carefully review security and privacy policies of any third-party tools a customer may choose to use, as once in the customer's hands the DNA data is no longer being used according to the 23andMe Privacy Policy. Notably, 23andMe's recent decision to limit developer access to their API (application programming interface) for raw genotype transfer, a mechanism relied on by several TPI tools (Nelson & Fullerton, 2018), further illustrates their desire to distance themselves from TPI tools they do not view as reputable or scientifically sound (23andMe, 2018c). A theme apparent in each of these companies' responses to TPI tools is that responsibility falls largely to the user. The DTC-GT companies are tasked with giving raw DNA "appropriate labeling that highlights its intended uses and limitations" (Personal Genetics Reps, 2018, sec. "Smash_Meowth" answered by "Dave from 23andMe"); however, beyond that the user must review and adjudicate among third-party websites they may want to use — placing the user at the center of this distributed system.

Third-party interpretation tools

The GDFs that customers can download from DTC-GT companies become the substrates for a heterogeneous set of TPI tools. In a structured content analysis of 23 third-party tools, I found a diversity of tool developers, types of information returned, and bioinformatic and analytic approaches to generating the information (Nelson & Fullerton, 2018; see also chapter 1). While most tools were created by commercial companies (n=15), five were developed by academics and three by non-specialists/citizen scientists. The companies ranged in size from small limited liability companies (LLCs) comprising only a few individuals to larger corporations (Inc. and Ltd.). Some DTC-GT companies also accept GDF upload from other DTC-GT companies (e.g. FamilyTreeDNA, WeGene, Athletigen, and DNAFit), putting them in the dual role of both GDF provider and third-party interpreter.

In terms of information returned, TPI tools can focus on one or any combination of genetic ancestry analysis, relative finding and genetic genealogy, health and wellness, and crowd-sourced citizen science research projects. One common thread among tools that return health or wellness information is reliance on publicly available literature and variant annotation databases, such as PubMed and ClinVar (discussed further below). Indeed, some of these tools are described by their developers as primarily a "literature search function" (Badalato et al., 2017) or, as I found in interviewing developers, as a "bridge to the literature" (Nelson & Fullerton, 2018). A good example of this bridging activity is Promethease, one of the more popular health-related tools (Wang et al., 2018; see also chapter 2). Promethease is built on top of the annotation wiki SNPedia. In addition to wiki users' manual contributions, SNPedia programmatically incorporates variant annotation information from sources such as ClinVar and PubMed. The number of reports a user receives from Promethease is therefore equal to the overlap of SNPs between their GDF and SNPedia entries, which can number in the tens of thousands (SNPedia, 2018). The content of a Promethease report[8] is essentially a reproduction of the SNPedia entry, including links to relevant publications; the user genotype at the SNP; and a disease risk associated with SNP (e.g., "2.5x risk for AMD"). Unlike a 23andMe report, for example, there is no aggregation or synthesis of information across multiple variants that may be associated with a particular health outcome. Not all third-party tools stop at bridging, however. The DNA Doctor smartphone app aggregates information across SNPs in a rather rudimentary way: by averaging risk estimates for related SNPs the developer has identified in SNPedia. Interpretome/GENOtation is a bit more sophisticated in its calculation of polygenic risk scores based on SNP sets previously published in scientific literature. The developers, however, emphasize the tool is meant to illustrate how genetic interpretation is done rather

[8] Example Promethease reports are available here: https://files.snpedia.com/reports/promethease_data/genome_Lilly_Mendel_v4_ui2.html (accessed Dec. 8, 2018).

than provide evidence of the user's actual risk (Nelson & Fullerton, 2018). In summary, the range of business models, types of reports, modes of generating reports, and claims about reports vary widely.

Variant annotation databases

Third-party tools draw upon publicly available literature and variant annotation databases to populate their reports, including the NHGRI GWAS Catalog, ClinVar, dbSNP, SNPedia, and PharmGKB. Though not always clear from how they are used in third-party services, the intent and scope of these databases vary. The GWAS Catalog began in 2008 as an NHGRI effort to make the fruits of GWAS research publicly available. It is a manually-curated database of significant findings from published GWAS and is fully accessible and searchable by the public. In 2015, the Catalog was redesigned and relocated from NHGRI to a website hosted by the European Bioinformatics Institute (Welter et al., 2014). As of November 26th, 2018, there were over 87,081 SNP-trait associations from 3,675 publications documented in the Catalog (see https://www.ebi.ac.uk/gwas/). While studies must meet specific quality metrics to be included in the Catalog, it is generally not meant to guide interpretation of individual genetic risk. Instead, example use cases fall under the umbrella of basic and translational research: "Catalog data are used by biologists, bioinformaticians and clinical/translational researchers as a starting point for further investigations to identify causal variants, understand disease mechanisms, and establish targets for novel therapies" (Welter et al., 2014).

Compared to the research focus of the GWAS Catalog, ClinVar is an annotation database geared towards clinical applications. ClinVar is maintained by the National Center for Biotechnology Information (NCBI) as an "archive for interpretations of clinical significance of variants for reported conditions" (Landrum et al., 2016). Database submissions come from a variety of entities, including clinical testing laboratories, research laboratories, the Online Mendelian Inheritance in Man database, and expert panels. As stated in the methods paper, "ClinVar variants have been observed in individuals and families, in either a research or clinical setting, and interpreted for their clinical significance relative to one or

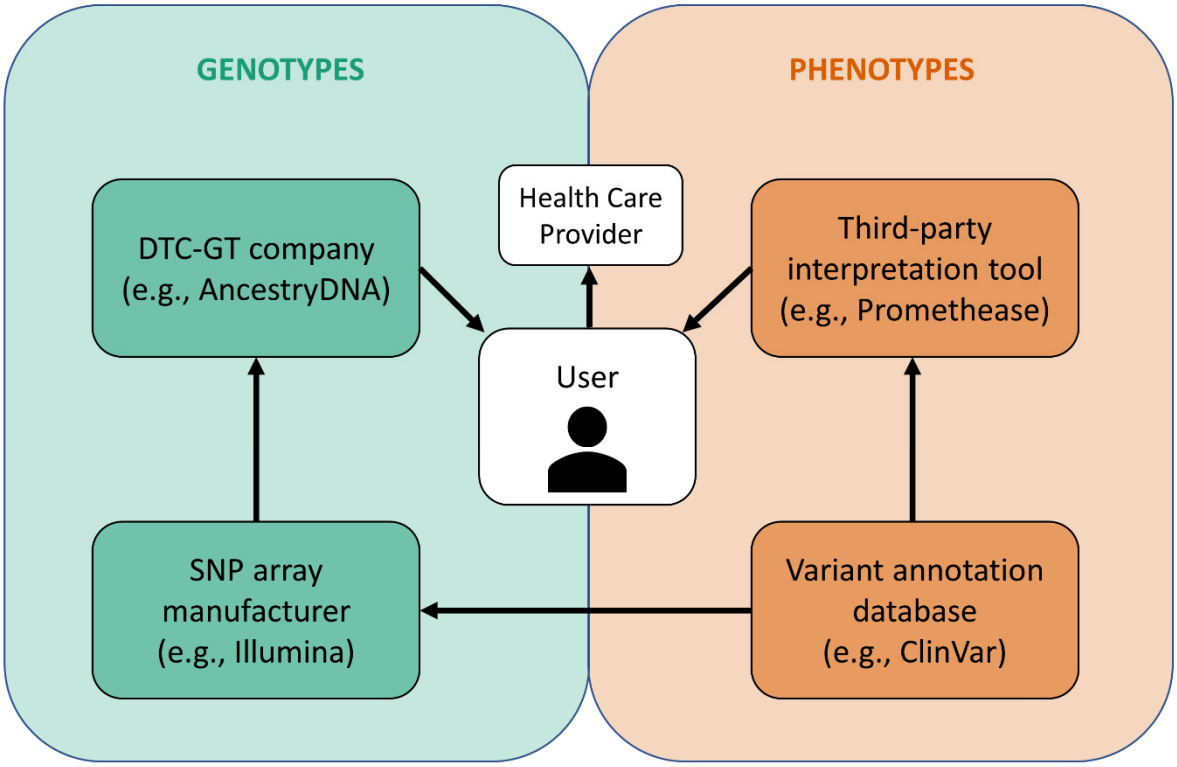
more disorders or to a set of clinical features and mode of inheritance" (Landrum et al., 2016). While submissions are manually reviewed by NCBI staff for administrative elements (e.g., condition names and database identifiers), the clinical significance is asserted and described by the submitter. ClinVar acts as an "archival system" in that a given entry can contain records from multiple submitters, which may provide conflicting information. As a remedy, ClinVar has encouraged the clinical genetics community to help refine the database with high-level curation; submissions from such expert panels take precedence over other submitters in the database. As of December 4th, 2018, ClinVar contained over 472,279 variation records with interpretation, 10,617 of which (2%) contained records from expert panels (ClinVar, 2018). Notably, the ClinVar home page includes a disclaimer noting that information on ClinVar is "not intended for direct diagnostic use or medical decision-making without review by a genetics professional," and that "[i]ndividuals should not change their health behavior solely on the basis of information contained on this website" (ClinVar, n.d.). As noted in the submission process overview above, the information submitted is not independently verified by NIH staff.

SNPedia is a crowd-sourced annotation wiki and, unlike ClinVar or the GWAS Catalog, is not maintained by a government entity. Instead, SNPedia began in 2006 by human geneticist Greg Lennon and programmer Mike Cariaso who met while working on the Human Genome Project. Variant reports on SNPedia are populated with a combination of manual and programmatic curation — i.e., computer programs or "bots" that routinely crawl through websites such as ClinVar and PubMed, searching SNP identifiers and extracting relevant information (Cariaso & Lennon, 2012; Nelson & Fullerton, 2018). Typically, one page is created per variant with three associated pages corresponding to the three possible genotypes for a bi-allelic SNP. Genotype-specific pages may have an associated odds ratio for each reported genotype-phenotype relationship. Inclusion criteria on the website FAQ note, "[a]nything for which we can find something worthy of recording," or more specifically that their "emphasis is on SNPs and mutations that have significant medical or genealogical consequences and are reproducible"

(SNPedia, 2018). Genotype-specific pages are typically only created from a published meta-analysis, a study of either 500 or more individuals or independent replication in a second population, or GWAS with p-values below the commonly used significance threshold of $5x10^{-8}$ (Cariaso & Lennon, 2012; SNPedia, 2018). Notably, while in the early days of GWAS meeting this p-value was sufficient, standards have since shifted to require independent replication and/or functional follow-up to publish GWAS (Kraft, Zeggini, & Ioannidis, 2009). Soon after creating SNPedia, Carioso and Lennon built Promethease as a companion software to retrieve SNPedia information and generate reports for users who upload their DTC-GT GDF.

Some in the professional genetics community might bristle at the thought of a crowdsourced wiki model of annotating variants; however, SNPedia creators view the open-sourced nature of the database as a benefit. The "diverse audience" of users can act as one layer of data curation, they contend, as they are "uniquely able and motivated to detect and report errors or nuances missed in the original research" (Cariaso & Lennon, 2012). Anyone is encouraged "jump in and give it a shot" to add or edit content on the wiki, as any changes made in error can be safely removed later (SNPedia, 2010). This collective monitoring of accuracy is the same production model that has given Wikipedia a reputation comparable to professionally produced encyclopedias, though the reputation is debated (Anthony, Smith, & Williamson, 2009). In the world of open source software, this sentiment is sometimes expressed as Linus's Law: "given enough eyeballs, all bugs are shallow" (Raymond, 2001, p. 30). Interestingly, this curation model is almost the inverse of the ClinVar database upon which SNPedia also draws. While ClinVar encourages expert panel review to assert clinical significance, SNPedia facilities contribution from a wide variety of non-experts, though these contributions are reviewed by SNPedia editors.

Figure 3.1. Schematic of the distributed system of TPI of raw genotypes from DTC-GT testing, with the consumer/user/patient at the center.



The components in context

Stepping back to look at each of these components in relation to each other reveals several salient points, as depicted in Figure 3.1. Starting at the bottom right of the figure and moving clockwise, variant annotation databases are used by SNP array manufacturers to select content for arrays (i.e., to select which variants to assay/genotype based on potential clinical relevance). SNP arrays are then used by DTC-GT companies, and the genotyping laboratories to which they may contract out, to genotype customer samples. DTC-GT companies make files of customers' raw/uninterpreted genotype data (the GDF) available for them to download. With the GDF in hand, users can upload their genetic information to TPI tools. TPI tools in turn can use information from variant annotation databases to provide reports back to consumers based on the specifics of their uploaded GDF. Therefore, the customer/user sits at the interface of potentially vast amounts of genotypic and phenotypic information and may be left largely to their own devices to make sense of it all. This is where HCPs may be implicated, i.e., if users bring TPI reports to their doctor for further explication and/or to address any concerns raised by the information.

Another feature of this system illustrated in Figure 3.1 is the cycle of information created by the reliance of both SNP array manufacturers and TPI tools on variant annotation databases. Specifically, this flow of information means that SNP arrays are likely to include variants with entries in these annotation databases, regardless of which variants were used in the DTC-GT company's formally reported interpretations and analyses. That TPI tools connect user genotypes to these same databases means that there is also likely to be substantial overlap between the SNPs in the GDF and the SNPs on which TPI tools can report back information. My assumption is that this cycle is largely unintentional and heretofore unrecognized — a side effect of the common use of publicly available annotation databases by different components in the raw data/TPI system.

Federal health regulations and other legal features of the policy landscape

Above I have described potential harms to consumers from false positives that make this area ripe for policymaking and introduced the various components that comprise the supply chain of raw genetic data and TPI. Next, I highlight some areas of regulation that should be informed by a fuller understanding of these scientific and technical aspects, focusing on health-related regulations administered by the FDA and CMS. Finally, under "Other issues" I briefly mention other areas that may be implicated: constitutional law and the First Amendment right to free speech and legal liability for false positives. This discussion aims to show how policymakers can employ knowledge of scientific complexity in their consideration of policy approaches to oversight of TPI. While this section is informed by regulatory language and guidances and secondary legal literature, it is not intended to be comprehensive or serve as legal advice or formal legal interpretation. Throughout I focus on consumers as a primary stakeholder group and protecting consumers from false positive results as the main policy problem; however, I also note where other stakeholder groups such as HCPs and health care systems may be impacted by potential regulatory outcomes.

FDA medical device regulation: GDFs and TPI tools

FDA regulation of medical devices could potentially apply to both DTC-GT companies, as raw data providers, and TPI tools. Under the authority granted in the 1938 amendment to the Food, Drug & Cosmetics Act, the FDA oversees medical devices — any "instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part or accessory…intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease" (21 U.S. Code § 321(h)). This oversight comes in the form of both premarket and postmarket review, the extent of which is based on the level of risk posed by the product (i.e., class I, II, or III device). The FDA's approach to regulating genetic testing has evolved over the past two decades, in response to both internal and external pressures to modernize the conception of a

device and how oversight should occur. While Palmer (2012) has noted that FDA might be the obvious choice to regulate DTC-GT in general, the area is in flux.[9] (For thorough historical reviews, see Spector-Bagdady and Pike (2014), and Palmer (2012)). Notably, DTC-GT companies offering only ancestry and genealogy information seem not to have come under direct FDA scrutiny, though there have been calls to regulate their accuracy and advertising (Lee et al., 2009).

A key question for policymakers is whether FDA oversight of DTC-GT companies as providers of interpreted reports can be extended to DTC-GT companies as providers of raw data (GDFs). In April 2017, 23andMe became the first DTC-GT company authorized by the FDA to sell genetic health risk (GHR) reports: initially 10 reports including risk information for Parkinson's, celiac disease, and hereditary hemochromatosis (FDA, 2017d). This authorization was granted through *de novo* premarket review, meaning that because the GHR reports were not similar enough to an existing authorized device, FDA reviewed data and information provided by 23andMe in several areas prior to granting the authorization. As summarized in the FDA press release (FDA, 2017d), the areas reviewed included evidence of genotype-phenotype associations reported in peer reviewed literature, studies that demonstrated 23andMe's ability to accurately genotype the variants associated with the given disease or condition, and a usability study that showed 23andMe's interpreted reports were easy for customers to understand.

The FDA authorization of this first set of 23andMe GHR reports accomplished at least three things. First, it established a new class II (intermediate risk) medical device, the "Genetic Health Risk

[9] Historically, FDA has exercised enforcement discretion regarding laboratory-developed tests (LDTs) or "home brews," which are tests done under the same roof of one laboratory or company. Notably, while LDT regulation is often discussed in the context of DTC-GT, several DTC-GT products may not actually qualify as LDTs given that genotyping is contracted out to a separate laboratory. In 2014, FDA (2014) articulated plans to increase its oversight of LDTs in a draft guidance. However, in 2017 FDA announced that final guidance would be delayed to enable further discussion among stakeholders and preparation by legislators (FDA, 2017c). Based on the analysis presented by Palmer (2012), it is unclear whether FDA will consider DTC-GT separately from LDTs, or whether it will fold DTC-GT regulations in with LDTs in the final guidance.

Assessment System," defined as a "qualitative *in vitro* molecular diagnostic system used for detecting variants in genomic DNA…that will provide information to users about their genetic risk of developing a disease to inform lifestyle choices and/or conversations with a healthcare professional" (FDA, 2017e). Second, it defined what is required of DTC-GT companies to receive marketing authorization for GHR reports. These requirements are called "special controls" and are meant to ensure the accuracy and reliability of the initially authorized GHR reports and similar reports in the future.[10] Third, by defining the new device class and establishing expectations via special controls, the FDA created a streamlined pathway through which subsequent GHR reports from 23andMe, or substantively similar reports from other DTC-GT companies, may be exempt from premarket review (i.e., can receive FDA authorization without going through the same, in-depth review process as 23andMe underwent to receive its first GHR authorization).

The extent to which the FDA's marketing authorization of 23andMe's interpreted reports and the new classification of the Genetic Health Risk Assessment System amount to regulatory scrutiny of the 23andMe GDF is an open question. A reading of the FDA's definition of this new generic device class suggests that only the variants going into the report are considered part of the device and would therefore not apply to the full GDF. For example, the 23andMe Personal Genome Service is described as the system "used for detecting clinically relevant variants in genomic DNA…for the purpose of reporting and interpreting Genetic Health Risks" (FDA, 2017e). Not surprisingly, the entirety of the GDF is not discussed as part of the product as doing so would have vastly increased the scope of evidence

[10] A full account of the required special controls for GHR tests is available in the FDA letter to 23andMe (FDA, 2017e). Examples of special controls include prominently labeling test limitations; using a sample collection device that has either been cleared, approved, or classified as exempt by FDA; and meeting specified genotyping accuracy thresholds. The special controls also stipulate what activities fall inside the scope of the special GHR category (e.g., informing lifestyle decisions in consultation with HCPs) and what falls outside the scope (e.g., prenatal testing or assessing cancer predisposition).

23andMe would have to provide to support its classification and that the FDA would have to in turn review. This interpretation of the GHR marketing authorization is consistent with 23andMe's customer-facing information about raw data, which notes that "only a subset of variants have been individually validated for accuracy" (23andMe, 2017a).

However, a conflicting conclusion could be drawn regarding FDA oversight of the full GDF based on FDA's definition of the Genetic Health Risk Assessment System. Specifically, the Genetic Health Risk Assessment System classification seemingly departs from FDA's definitions of other medical device classifications, which are "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease" (21 U.S. Code § 321(h)). In contrast, the GHR approval distinguishes the genetic *risk* information provided from diagnostic results. The "device does not determine the person's overall risk of developing a disease;" it may, however "inform lifestyle choices and/or conversations with a healthcare professional" (FDA, 2017e, p. 3). This definition suggests that FDA's conception of a device can include non-diagnostic information that can become part of a chain of events leading to diagnostic or other medical decision-making. Therefore, either a full GDF or TPI tool could also potentially be considered devices within FDA jurisdiction, given that they can precipitate a similar chain of events without providing diagnostic information directly.

The relevance to GDFs of the FDA's marketing authorization of 23andMe interpreted reports seems even less clear when considering GDFs from ancestry and genealogy DTC-GT companies. Specifically, GDFs that are at least partially involved in an FDA-authorized test form the minority of GDFs: currently only those from 23andMe and perhaps soon those from other DTC-GT companies returning health reports classified as Genetic Health Risk Assessment Systems. However, the largest market share for DTC-GT remains ancestry and genealogy related tests, with over 10 million customers having access to raw data from AncestryDNA (AncestryDNA, 2018a) and 1.2 million from MyHeritage in under two years (Zhang, 2018). Could knowingly providing GDFs that lead to the return of health

information from TPI tools focus FDA attention on an ancestry- or genealogy-based DTC-GT company? There is precedent for FDA scrutiny of players upstream of the interpreter, as evidenced by the FDA's 2010 warning letter to Illumina regarding their manufacturing of the array used by 23andMe and deCODE. The mere act of "knowingly providing" (FDA, 2010) arrays to these DTC-GT companies was sufficient in the FDA's view to implicate Illumina in the DTC-GT companies' lack of compliance with medical device regulation. Similarly, moving down the supply chain, a DTC-GT company that provides customers with data that is used in a health-related TPI tool could potentially be implicated in non-compliance with medical device regulation. Notably, in a 2010 *Newsweek* interview, FDA officials Alberto Gutierrez and Elizabeth Mansfield were asked whether a DTC-GT company would "need to be approved [by FDA] just to provide a raw SNP list to people" (Carmichael, 2010, para. 15). Mansfield responded, "They would if they made medical claims about that data. If they don't make any medical claims about that data, then they're free to provide information as far as we're concerned" (Carmichael, 2010, para. 15). DTC-GT companies typically do not make medical claims about the GDF files they provide to customers, e.g., both 23andMe and AncestryDNA describe the raw data as not for medical or diagnostic use (23andMe, 2017a; Personal Genetics Reps, 2018). Therefore, according to Mansfield's comment, DTC-GT companies should not need FDA authorization solely to provide GDFs.

Moving onto the TPI tools themselves, there are again questions about whether they could meet the regulatory definition of a medical device as defined in 21 U.S. Code § 321(h). These interpretation-only tools vary widely in terms of the information given and the way that information is generated. Developers of these tools often express doubt that their activities would attract FDA regulation, as according to developers they are "bridging to the literature" via linking user genotypes to

publicly available information sources rather than providing direct interpretation[11] (Nelson & Fullerton, 2018). For example, Promethease developers consider their service to be beyond FDA reach, and they have argued that any regulation of Promethease would by analogy also require shutting down WebMD and Wikipedia (Regalado, 2014). In the 2010 interview mentioned above, FDA officials Gutierrez and Mansfield were asked whether simply pointing a user to a research paper could be considered a "medical claim," to which Gutierrez replied, "It depends" (Carmichael, 2010, para. 16). In the 2014 article about Promethease noted above, an FDA official said the agency did have "authority to regulate software that interprets genomes" (Regalado, 2014), which would suggest FDA could regulate TPI tools such as Promethease (potentially dependent upon definitions of "software" and "interprets"). While not mentioned explicitly, it is possible this official was referring to "Software as a Medical Device" regulation, discussed below.

FDA Digital Health Innovation Plan and Software as a Medical Device

The FDA has taken steps to modernize its approach to regulating health technology that may be relevant when considering potential oversight of TPI tools. In announcing its "Digital Health Innovation Plan" (DH Plan) in June 2017, FDA Commissioner Scott Gottlieb articulated the Agency's responsibility to "promote and encourage safe and effective innovation" and to remove regulatory ambiguity that stifles innovation (Gottlieb, 2017). A notable component of the DH Plan is clarifying types of digital health technologies, including software, that the FDA does *not* plan to regulate (FDA, 2017b). The DH Plan was

[11] In interviews presented in chapter 1, developers' comments about potential regulation did not appear to be tied to any specific regulatory definition(s), e.g., developers did not explicitly relate the distinctions they perceived between "bridging" versus interpretation to the FDA definition of a medical device.

partly motivated by the 21st Century Cures Act ("Cures Act"), enacted by Congress in December 2016, in which section 520(o) was added to the Food, Drug, & Cosmetics Act to describe software functions that are excluded from the medical device definition. As part of the DH Plan and overall coordinated response to the Cures Act, in December 2017 FDA issued draft guidance[12] articulating the Agency's interpretation of the amended device definition and how it plans to incorporate it into previously issued guidances (FDA, 2017a). For example, according to the December 2017 draft guidance, FDA plans to clarify how the Cures Act affects prior FDA guidance on mobile medical apps regulation and low risk general wellness products. Other components of the DH Plan include a novel pre-certification program that would evaluate companies (e.g., software developers) rather than individual products so as to minimize or eliminate (for low risk devices) premarket review of new products (FDA, 2017b). A common element across these regulatory updates is broadening the conception of medical devices from primarily physical objects to include software, algorithms, and smartphone apps — a regulatory shift that could potentially categorize genetic interpretation services and therefore TPI tools as medical devices.

The scientific and technical features of TPI tools can guide considerations of whether those returning health-related information (e.g., Promethease or Livewello) could be considered Software as a Medical Device (SaMD). These tools exist online as interpretive algorithms that link users' raw genotypes with existing annotation databases to produce a report. Across the board, TPI tools returning health or wellness information state that the information returned is for educational, informational, and research purposes and is not meant to be used for medical or diagnostic purposes. In comparison, SaMD is

[12] The draft guidance, "Changes to Existing Medical Software Policies Resulting from Section 2060 of the 21st Century Cures Act," was issued on December 8, 2017 and was open to a 60-day comment period ending February 6, 2018. As of December 8, 2018, no final guidance has been issued.

defined as "software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device" (FDA, 2018b). The International Medical Device Regulators Forum Working Group on SaMD[13] elaborates that SaMD is "software that utilizes an algorithm (logic, set of rules, or model) that operates on data input (digitized content) to produce an output that is intended for medical purposes as defined by the SaMD manufacturer" (Software as a Medical Device Working Group, 2017). Parsing this definition, there is (1) an algorithm operating on (2) input data to (3) produce output that (4) the manufacturer intends for use in medical purposes. Third-party tools satisfy (1)-(3), even if the "algorithm" is something as straightforward as cross-linking a user's genotype at one SNP with the corresponding SNPedia report, as done by Promethease. Other tools' algorithms are more complex, such as Interpretome/GENOtation and DNA Doctor, which combine information across SNPs to produce an aggregate score (e.g., polygenic risk score). However, TPI tools seem to depart from the SaMD definition at item (4) in that developers explicitly do not intend for their use in medical decision-making. If each of the four elements of the parsed SaMD definition is required to be classified as SaMD, then it does not appear that the FDA would view TPI tools as SaMD.

Ultimately the FDA may consider TPI tools to be low risk, general wellness products and therefore outside FDA jurisdiction. Indeed, a component of the Cures Act was to exclude general wellness products from the medical device definition such that the FDA would not be responsible for oversight. Specifically, the updated definition of a medical device (FDCA 520(o)) excludes software "for maintaining or encouraging a healthy lifestyle and is unrelated to the diagnosis, cure, mitigation,

[13] The International Medical Device Regulators Forum is a "voluntary group of medical device regulators from around the world who have come together to reach harmonization on medical device regulation" (FDA, 2018b). In 2013, the Forum created a working group on SaMD, chaired by FDA, that has since developed internationally recognized and adopted (including by FDA) documents on various aspects of SaMD, including key definitions and a plan for clinical evaluation. FDA has issued Forum documents as guidance with the stated intent to "consider the principles of [the] guidance in the development of regulatory approaches for SaMD and digital health technologies" (Software as a Medical Device Working Group, 2017, p. 2)

prevention, or treatment of a disease or condition" (FDA, 2017a). As FDA laid out in its final guidance on low risk, general wellness products (FDA, 2016), encouraging a "healthy lifestyle" means promoting "a general state of health or healthy activity." The guidance states that wellness products may either promote health in general or a healthy lifestyle targeted at reducing risks of certain chronic diseases or conditions, "where it is well understood and accepted that healthy lifestyle choices may play an important role in health outcomes for the disease or condition." In summary, the FDA does not plan to review low risk, general wellness products such that they can be legally marketed to consumers without FDA oversight.

The vast amount of information potentially returned to a TPI user may complicate applying the definition of general wellness products to TPI tools and therefore pose a problem in determining whether TPI tools fall under the general wellness guidance and therefore outside FDA jurisdiction. Promethease is a good example, as it returns information on far more than just chronic diseases with well-known and accepted risk-reducing lifestyle choices. For example, Promethease reports can include a variant associated with Huntington's disease, a neurodegenerative disease without well-known, risk-reducing lifestyle choices (Myers, 2004). This single genotype-phenotype association is one of over 20,000 available[14]; determining whether any given association is for a chronic disease with possible risk-reducing behaviors would be a daunting task for either FDA or for a TPI tool developer potentially trying to justify classification of their tool as a low risk, general wellness product outside of FDA jurisdiction. Similarly, with Livewello customers can generate reports based on any SNP(s) in the GWAS Catalog. In trying to determine if TPI tools could be classified as general wellness products, it would likely be

[14] The example Promethease report previously noted, at https://files.snpedia.com/reports/promethease_data/genome_Lilly_Mendel_v4_ui2.html, includes 26,407 individual results (genotype-phenotype associations). The exact number can vary for any given user and is determined by the number of SNPs overlapping between the user's GDF and SNPedia entries. The Huntington's disease variant noted above is rs1805323 (see https://www.snpedia.com/index.php/Rs1805323).

difficult for FDA (and potentially for TPI tool developer themselves) to fully know the types of information returned by these tools because that information is dynamically tied to the underlying databases that populate them.

FDA recognition of variant annotation databases

On April 13th, 2018, the FDA issued final guidance on a mechanism to recognize publicly-available variant annotation databases, which can be leveraged as "sources of valid scientific evidence" in FDA's regulatory review of next-generation sequencing (NGS) and other genetic tests (FDA, 2018c). The motivations behind this mechanism are two-fold: (1) to encourage the deposition of genotype-phenotype information into publicly available (vs. proprietary) databases and (2) to ease the burden on genetic test developers seeking marketing authorization for tests that rely on information in already recognized databases, in that information from such databases can be used as evidence of clinical validity during premarket review (FDA, 2018c, p. 5). There are at least two potential implications of this voluntary database recognition program for TPI. First, the databases that TPI tools use (e.g., ClinVar, SNPedia, GWAS Catalog) have the option to undergo the recognition process with the FDA and thus potentially gain some stamp of legitimacy from the Agency. Second, TPI tools that use FDA-recognized databases in their interpretations would presumably have a smoother path to FDA authorization if it were to be required (e.g., if they were to be considered SaMD and not low risk, general wellness products), as tools would not have to separately generate evidence of clinical validity for genotype-phenotype associations extracted from FDA recognized databases.

In the guidance, FDA makes recommendations in four areas to support recognition: database procedures and operations, data quality, variant evaluation and assertions, and professional training and disclosure of conflicts of interest. Notably, under variant evaluation and assertions, FDA recommends that "each variant evaluation should be performed by at least two qualified and trained professionals to

lessen the risk that any single assertion could be incorrectly made" (FDA, 2018c, p. 11) and that "assertions include descriptive language about a variant such as clinically significant, pathogenic, benign, likely pathogenic, likely benign, variant of unknown significance, etc." (FDA, 2018c, p. 12). A plain reading of these recommendations suggests that, among the databases commonly used in TPI tools to date, ClinVar may be the only viable candidate for FDA recognition.[15] ClinVar has some mechanism for expert panel review and already uses variant classifications similar to the recommended descriptive language. In contrast, the GWAS Catalog — while manually curated — does not include either of these features, and indeed is unlikely to pursue FDA recognition given its research focus. SNPedia is more unusual in that it blends crowd-sourced annotations from experts and non-experts alike with programmatic integration of ClinVar. Notably, SNPedia assigns a binary color code of red equals "bad" and green equals "good"/protective and displays an associated risk level, rather than the classification scheme recommended by the FDA (pathogenic, likely pathogenic, benign, etc.). According to the guidance, SNPedia could seek recognition for the subset of its database that links directly to ClinVar, but the utility of that is unclear given that it would essentially amount to recognition of ClinVar itself.

A potential impact of FDA recognition for TPI developers is the signaling of which databases are most useful or authoritative for populating their reports. The heterogeneity of databases used by TPI tools suggests that developers may select databases based on other features besides clinical validity. These features may include ease of use, precedent in other TPI tools, and availability of programmatic interface (e.g., API); indeed, the results of interviews with tool developers described in chapter 1

[15] On December 4th, 2018, ClinGen Expert Curated Human Genetic Data became the first database to receive FDA recognition (FDA, 2018a). ClinGen and ClinVar have a close relationship in that ClinVar serves as the "primary site of deposition" for ClinGen's expert curations (see https://www.clinicalgenome.org/about/about-the-clingen-and-clinvar-partnership/). However, this FDA recognition of ClinGen does not appear to equate to FDA recognition of ClinVar as a whole, as only a subset of ClinVar entries are deposited by the ClinGen resource (i.e., the subset of ClinVar entries with a review status of "reviewed by expert panel").

highlight the importance of these features to developers. For example, openSNP ranks selected information sources on availability of publicly available source information (i.e., open access publications) and the use of "plain English" variant summaries (Greshake et al., 2014). The prioritization of source information by tool developers can be influenced both by their values (e.g., openSNP values open source information) and their expertise (e.g., a developer with a background in smartphone development instead of genetics may prioritize databases with easily integrated APIs). Once variant databases begin to receive FDA recognition, this could provide a new system of prioritization for tool developers — one that might ultimately improve the reliability and quality of their interpretations entirely separate from questions of whether TPI tools fall under FDA oversight.

Laboratory certifications: CLIA and CAP

Laboratory certification programs are another area of health-related regulation that may be relevant for the GDF raw data component of the TPI supply chain. Laboratory certification is important for establishing and enforcing minimum standards to ensure quality at multiple stages of laboratory testing, including sample handling, test performance, and post-test interpretation and results delivery. CLIA certification lays minimum standards of proficiency for laboratory personnel and accuracy for the laboratory procedures. CLIA is administered by CMS and issues certificates to clinical laboratories, defined as facilities that test human samples "for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings" (Javitt & Carter, 2014). Laboratories often seek additional certification from the College of American Pathologists (CAP), which has developed disciplinarily specific checklists for laboratory activities such as molecular pathology and forensic testing (Vance, 2007). CAP certifications are more stringent than CLIA, with over half of CAP's requirements exceeding the CLIA minimum standard. Notably, CLIA has no specific regulatory infrastructure for genetic testing. Both 23andMe and

AncestryDNA contract genotyping out to CLIA- and CAP-certified laboratories: 23andMe to LabCorp and AncestryDNA to Quest Diagnostics. FamilyTreeDNA operates its own CLIA- and CAP-certified laboratory in Houston (Gene by Gene, n.d.), which is also the lab used by MyHeritage (MyHeritage, 2017).

Laboratory certification is only likely to affect the raw genetic data/TPI supply chain at the site of the clinical laboratory itself — the raw data generator (e.g., LabCorp or Quest Diagnostics). According to Javitt and Carter (2014), CLIA certification would require specific training and education for personnel carrying out genetic interpretation as part of laboratory services. However, if interpretation is occurring outside the laboratory, as with TPI, CLIA certification would not provide oversight for the personnel or laboratory protocols involved in the interpretation. CLIA certification could provide some quality assurance in the generation of the raw genetic data and thus represent some measure of quality control for the GDF as a whole, but it is unlikely the accuracy of specific genotypes would be evaluated. It is also probable that the DTC-GT company does some of the quality control once the data are delivered from the testing laboratory. For example, LabCorp may perform a general quality control of genotyping batches which are then returned to 23andMe for an additional layer of quality control, albeit in the latter setting focusing only (or primarily) on the specific variants included in the interpreted reports.[16]

In summary, laboratory certification is unlikely to ensure the accuracy of raw genotypes in a GDF to a very high degree (and not for specific variants) and would have essentially no regulatory reach to third-party interpreters. Compared to FDA marketing authorization, e.g., CLIA is also a much lower regulatory hurdle to clear. In a PLOS Genetics interview soon after its first FDA marketing authorization for carrier status reports, 23andMe Chief Executive Officer Ann Wojcicki noted that FDA standards were higher than CLIA "in every sense" and that it "is a lot more work to get an FDA clearance than CLIA: the

[16] While such a protocol is not easily findable among DTC-GT companies' public-facing information, it is a model familiar to me from doing GWAS data cleaning at the University of Washington Genetic Analysis Center.

amount of validation, the amount of user testing" (Gitschier, 2015). CAP may have more stringent and specific requirements for genetic testing laboratories compared to CLIA, but those requirements would again be unlikely to reach TPI services as they do not operate clinical laboratories. Additionally, DTC-GT companies focusing on ancestry and/or genealogy are not required to use certified clinical laboratories for genotyping since they are not providing information related to health or disease. Ultimately, those companies may find it economically attractive to do so, however, in part to attract customers with the stamp of approval such accreditations represent. But this is no guarantee that newcomers to the DTC-GT ancestry/genealogy industry will follow suit. Ultimately, CLIA- and CAP-certification of DTC-GT genotyping laboratories may not protect consumers from false positives that result from TPI of incorrect raw genotypes, and even less protection would exist for those DTC-GT companies providing GDFs not generated in CLIA- or CAP-certified environments.

Other issues

In addition to the health regulations described above, there are other areas of law that could be informed by a fuller understanding of TPI. Next, I briefly discuss two such areas and raise questions for future analyses: constitutional law and the First Amendment right to free speech and legal liability for false positives.

Two key questions when considering how the First Amendment might affect regulation of TPI are likely (1) whether either GDFs or TPI reports could be considered speech and (2) if yes, whether they would be considered "commercial" or "non-commercial" speech. A full analysis of these questions would benefit from prior work of legal scholars in related areas. Specifically, the possibility of First Amendment challenges to regulation has been examined in the context of return of results to participants in biomedical research (Evans, 2014), advertising of DTC-GT services (Javitt, Stanley, & Hudson, 2004), and — to some extent — TPI of DTC-GT data (Spector-Bagdady & Pike, 2014). Notably,

whether facts or data can be considered speech was addressed by a U.S. Supreme Court case in 2011. In *Sorrell v. IMS Health*, a Vermont state law seeking to limit the sale of aggregate data on drug prescriptions was struck down as a First Amendment violation. The Court's ruling held that facts and information, as the starting point for the kinds of speech "essential to advance human knowledge," are in themselves a kind of speech and should enjoy the same opportunity for First Amendment protections as the more familiar kinds of speech they help create (*Sorrell v. IMS Health*, 564 U.S., p. 15 (2011)). Palmer's analysis of this case concludes that if drug prescription data can be considered speech, "then a file of SNP genotypes, or a whole genome sequence, could likewise be speech" (Palmer, 2012, p. 515).

Considering First Amendment protections requires distinguishing between different types of speech, which are afforded different levels of protection accordingly. Classifying GDFs and TPI reports would therefore be necessary when considering the extent to which they would be protected by the First Amendment. For example, defamation or incitement are not protected (i.e., are regulable) while core speech, such as political speech and scholarly debate, receives the highest levels of protection. Germane to the personal genomics context, Javitt, Stanley, and Hudson (2004) indicate that speech is equally protected regardless of whether it is detrimental to the health of an individual or population.

One key question in determining First Amendment protections of GDFs and TPI would be whether they are considered commercial or non-commercial speech. This determination may be complicated by the fact that several TPI tools are run by individual citizen scientists rather than traditional companies. If viewed as commercial speech, attempts to regulate them (e.g., by the FDA) would be subject to what is known as the *Central Hudson* test, a standard established by the U.S. Supreme Court to constitutionally evaluate restrictions on commercial speech. Evans (2014b) explains that the *Central Hudson* test involves first determining whether the commercial speech is either misleading, deceptive, or relating to illegal activity — if yes, the speech is not protected and therefore can be regulated without any heightened scrutiny. If not, the next steps are to assess whether the

proposed regulation specifically advances substantial government interest, and in no more a restrictive way than is necessary to advance the given interest. Such an analysis of GDFs and TPI reports would therefore need to ask whether their contents would be considered misleading and then subsequently to delineate what the government interests would be in regulating them (e.g., consumer protection or reducing health care costs). The government could even have conflicting interests regarding consumer use of TPI tools. Specifically, recent law enforcement use of consumer-oriented genetic genealogy databases such as GEDmatch has led to the solving of over a dozen cold cases (Erlich, Shor, Pe'er, & Carmi, 2018), suggesting that an argument could be made for government having an interest in encouraging use of TPI tools. The more GEDmatch users, the more likely that investigations using the database will be able to identify a suspect or their relatives.

Errors that arise from TPI of DTC-GT raw data may also prompt legal action. Who will be legally at fault when a customer receives, for example, a false positive (e.g., see Almendrala, 2018; Hercher, 2018; Kolata, 2018a), and therefore who will be held legally responsible for compensating individuals harmed by those errors? The bifurcation between the genotypic and phenotypic information (see Figure 3.1) will make this question challenging to answer. Addressing this legal issue would likely involve aspects of contract law, tort law, and state laws about the practice of medicine. Relevant case law in this area might include *William v. Athena*, discussed in the context of legal liability for variant interpretation by Thorogood, Cook-Deegan, and Knoppers (2017). In that case, the South Carolina Supreme Court decided that the genetic sequencing company Quest Diagnostics was acting as a licensed HCP and therefore could be sued for medical malpractice ("South Carolina Supreme Court Decision Deals Blow to Plaintiff in Quest Wrongful Death Suit," 2018). While genotyping laboratories producing DTC-GT GDFs are acting in a different context — i.e., generating genetic data for DTC-GT consumer products rather than for a clinical diagnostic sequencing test, that a sequencing or genotyping laboratory could be considered a HCP in this specific case suggests that laboratories generating DTC-GT GDFs could

potentially also be considered HCPs and held legally liable for TPI false positives. Consumer protection laws may also be implicated and are subject to enforcement by the federal government through the Federal Trade Commission and states' attorneys general. Overall, the decentralization of responsibility in the raw data/TPI tool supply chain may make it more difficult to pinpoint responsibility for misleading claims that result in a negative outcome for consumers.

Discussion

The distributed system of raw personal genetic data and TPI (see Figure 3.1) and the heterogeneity present within each component make it challenging to determine appropriate and effective policy responses. Ideally safeguards would be in place to avoid harm to consumers from false information, whether stemming from incorrect raw genotypes provided by DTC-GT companies or from faulty interpretation of accurate genotypes by TPI tools. Policymakers have a difficult job in understanding the scientific and technical details of the components and then applying this knowledge to identify appropriate and effective policy responses. As laid out in the section on components, the distinctive features of DTC-GT raw data and TPI that make this challenging include the separation between elements in the supply chain, where each is necessary but not sufficient to provide a third-party interpreted result to the user; the volume and heterogeneity of information provided by TPI tools; the changing nature of information provided by tools from linking to dynamic databases of scientific literature and human variation; and the variety of business models represented among tools. Additionally, any policymaking in this area is further complicated by the need to balance a complex set of ethical concerns (Childress et al., 2002), including respect for individual autonomy by allowing individuals to pursue interpretation of their genetic data; just allocation of finite health care resources — the concern that broad availability of TPI and the potential for false positives may precipitate

excessive follow-up testing and appointments with providers; and to minimize harms in the least restrictive way possible (Childress et al., 2002)

In the section on federal health regulations, I explored aspects of the U.S. federal regulatory landscape that could potentially apply to DTC-GT raw data and TPI tools, focusing on health-related regulation administered by the FDA and laboratory accreditation overseen by CMS. I described difficulties fitting either DTC-GT GDFs or TPI tools into existing regulatory mechanisms. For example, the full GDF appears to be excluded from the new device class established for 23andMe GHR reports, the Genetic Health Risk Assessment System, which instead encompasses only the variants used in the interpreted reports. TPI tools could potentially be considered SaMD and therefore under FDA jurisdiction; however, that such tools are typically not intended for medical use by developers could exclude them from the SaMD definition. If considered low risk general wellness products, TPI tools would fall outside FDA purview, but this determination is complicated by the scope of available health/wellness information and the fact that information in TPI reports may be dynamically tied to underlying literature and annotation databases. Laboratory accreditations such as CLIA and CAP may establish some minimum standards for the laboratories that produce GDFs, though this is unlikely to ensure the accuracy of raw genotypes in a GDF to a very high degree (and not for specific variants) and would have essentially no regulatory reach to third-party interpreters. Given the legal precedent that data and information can be considered speech protected by the First Amendment, any regulations constraining the provision of GDFs or TPI reports (e.g., by FDA) could be subject to a First Amendment challenge.

Notably, the policy challenges posed by a separation between data provider and data interpreter are not unique to the DTC-GT genomics context. In the NGS industry, many “single segment” companies focus on one part of the supply chain versus integrating across all steps (Evans, 2014a). In a web-based analysis of 68 NGS companies, Curnutte et al. (2014) found roughly half of companies were

involved in only sequencing or only interpretation. They observed that "this fragmentation of sequencing and analysis in nearly half of the companies we examined may make regulation of devices that only perform one function or the other difficult because neither function on its own currently constitutes a medical test" (Curnutte et al., 2014, p. 982). Members of the professional genetics community disagree, however, on how interpretation-only services fit into the regulatory landscape. In a Delphi panel of 48 genetics professionals across a range of stakeholder groups for clinical NGS, Messner et al. (2016) found that 40% of panel participants thought interpretation-only services are subject to FDA regulation, and 63% thought such services constituted the practice of medicine. This lack of consensus among genetics experts highlights the complexity of identifying and operationalizing policy responses to interpretation-only tools.

Here I have presented a scientist's perspective on the components individually, the relationships between them, and issues that policymakers should be aware of when evaluating the applicability of existing or future regulations. The analyses here are not meant to be comprehensive but rather to illustrate how understanding the science can inform policymakers and legal scholars moving forward. Future research should explore potential regulation by the U.S. Federal Trade Commission, as well as other levels of regulation including state and local within the U.S. and also the broader global context.

CONCLUSION

Over the course of this project, I have obtained a substantial amount of empirical data by examining third-party interpretation (TPI) tools, interviewing tool developers, surveying and interviewing direct-to-consumer genetic testing (DTC-GT) customers and TPI tool users, and reviewing regulations and legal literature to identify relevant policy challenges. Below I summarize my unique scientific contributions, identify avenues for further research, and conclude with recommendations for moving forward.

Summary of scientific contributions

My research has yielded several unique contributions to the study of DTC-GT raw data usage and TPI. To my knowledge, I produced the first systematic, in-depth characterization of a diverse landscape of TPI tools (chapter 1). In a relatively short time since publication in the *Journal of Genetic Counseling*, this work has been cited by two articles in high profile journals: *Science* (Erlich et al., 2018) and *PLOS Biology* (Guerrini, Robinson, Petersen, & McGuire, 2018). Through interviewing tool developers, I identified a novel distinction between "bridging to the literature" and interpretation. However, when I compared developers' comments to my content analysis results of what tools actually do and how, I concluded that the claimed distinction between bridging and interpretation is in fact more blurred and nuanced than developers' comments conveyed. Instead, tools vary in their approaches, and there is a spectrum between bridging and interpretation. Furthermore, developers' claims about bridging may be at least partly motivated by regulatory concerns rather than a commitment to bridging *per se*.

Chapter 2 includes the largest known survey to date of DTC-GT customers' broad use of raw data and TPI tools. Indeed, only one other survey has been published on these topics (Wang et al., 2018) and asked a less detailed set of questions in a smaller sample size (478 versus 1,137 DTC-GT customer respondents to my survey). With my survey and follow-up interview data, I generated novel insights into

the use of multiple tools across the domains of health, ancestry, and genealogy. For example, users of exclusively health- or exclusively non-health related tools differed significantly from each other and users of both tool types in terms of demographics, DTC-GT tests ordered, and DTC-GT testing motivations. In follow-up interviews with tools users, I observed how respondents came to use tools across both health and non-health domains, driven by general curiosity and the sharing of information on social media hubs such as Facebook and Reddit.

In chapter 3, I contributed a unique description of raw data and TPI as a distributed, supply chain system, which highlighted technical and scientific aspects that will be relevant for policymakers considering potential regulation in this space. My analysis highlights the interconnectedness of the various components in the system and how the same sources of genetics knowledge (e.g., the peer-reviewed literature and variant annotation databases) can feed into these different components (e.g., genotyping array design and TPI reports). In examining potential regulatory definitions from the FDA (i.e., Genetic Health Risk Assessment System, Software as a Medical Device, and low risk general wellness products) and CMS, I concluded that existing regulatory mechanisms do not cleanly fit either DTC-GT raw data or TPI tools and indeed may be constrained by First Amendment free speech protections.

Finally, my overall approach of sequentially studying tools, users, and policies has allowed for a more informed, integrative set of analyses and insights across these areas. I have also brought to bear a unique combination of domain expertise in genetics and ethical, legal, and social implications, which results from my parallel training in Public Health Genetics and 14 years working in human genetics research. I have also deployed both quantitative and qualitative research skills in chapters 1 and 2 — a mixed methods approach that has yielded deeper, more nuanced insights than either methodological approach likely would have on its own.

Throughout this process I have repeatedly asked myself, and been asked by mentors and friends, what I think *should* be done to minimize potential harms and maximize potential benefits from the use of raw personal genetic data in third-party tools. Potential harms to TPI tool users include emotional distress and financial hardship in following up on false positive results — which can also lead to unnecessary consumption of limited health care resources — and general confusion and misunderstanding when faced with a large volume of information (e.g., over 20,000 genotype-phenotype associations in a Promethease report). In the sample of DTC-GT customers who took my survey and participated in follow-up interviews, the evidence of these potential harms was largely lacking, or at least seemed to occur far less than benefits perceived by users. Potential benefits include promoting autonomy and individual choice (i.e., to do what one pleases with one's own genetic information), increasing scientific and genetic literacy, and enjoyment of pursuing genealogy and ancestry information (e.g., for building family trees). Two-third to three-fourths of survey respondents agreed that using TPI tools increased their understanding of genetics in general or of how DTC-GT companies interpret genetic data, which seems beneficial unless we suspect those understandings are actually faulty and counterproductive. Only 6% of respondents reported feeling upset by the information they received, and only 15% were motivated to see a health care provider (notably, that rate increased to 29% among those responding based on Promethease). In qualitative survey data from open text responses, there were certainly some instances of negative outcomes, including difficulty understanding the data, needing more support, and fear caused by learning about risk of potentially deadly disease. These experiences should not be discounted even if they were not reported by many respondents.

Among interviewees, I had the opportunity to glean even more information about their experiences using TPI tools. For those who brought in their TPI reports to health care providers, it was often because the information corroborated some known family health risk or other preexisting health

concerns. This is arguably a benefit if it precipitated a useful conversation between the user/patient and the provider, even if the TPI report was only a "genetic icebreaker." Another important observation from my interviews was that users often had a rather sophisticated understanding of the limitations of TPI tools and were able to distinguish between more and less trustworthy tools. (Though I think most people would be suspicious when they see an advisory board that consists of one former Mr. USA (NutraHacker, n.d.).) These observations also do not lead to the conclusion that all tool users are able to make such assessments, or even that these assessments are completely accurate. Though in our consumer-oriented, online culture, daily we are tasked with distinguishing between legitimate and illegitimate claims and products. Sequestering decisions about TPI tool use off into a corner of heightened scrutiny may just be another example of genetic exceptionalism (Sulmasy, 2015).

Recommendations

Since I started this project in 2014, there has been more attention paid in both public and academic spheres to potential harms from TPI, which has led to some proposed remedies. First, in September 2018, 23andMe changed its API (application program interface) policy to restrict what can be accessed and by whom (23andMe, 2018c). Since 23andMe launched its API in 2012, any app or TPI tool developer could use the API to allow 23andMe customers to grant the app permission to access their raw genotypes. Under the new policy, however, only 23andMe's scientific research collaborators can use the API to access raw genotypes. Apps that meet 23andMe's scientific and privacy standards, which they have yet to announce, will be allowed to access customers' interpreted reports to build upon or extend with the app, but not raw genotypes. To me, it seems clear that 23andMe made the change because they do not want to endorse or promote third-party apps that are not scientifically valid and/or do not meet basic privacy standards — perhaps given some of the bad press around false positives (e.g., see Almendrala, 2018; Hercher, 2018; Kolata, 2018b) and law enforcement use of third-party genealogy

databases (Erlich, Shor, Pe'er, & Carmi, 2018). But customers can still download their full raw data file and upload to any TPI tools that do not rely on the API.

An unintended consequence of this change is that 23andMe customers are potentially exposing more of their data to third parties. Whereas with the API apps might previously have only taken the subset of SNPs needed for their program, now customers will have to provide their whole file. Also, instead of securely transferring the genotypes via the API, the customers' raw data file is only as secure as their own personal computing device(s). 23andMe might still be concerned with these implications, but it shows how the API policy change can in some ways run counter to the company's stated goals of enhancing customer privacy. A preferable response from 23andMe would be to publicly articulate their scientific and privacy standards and then to potentially list the tools that do and do not meet them. The API policy changes are doing this, but only indirectly and in a way that may not actually empower customers to make better uses of or decisions around their raw data.

Another recently proposed solution to the privacy issues of raw data availability was made by Erlich and colleagues (2018). The Golden State Killer case was solved by law enforcement being able to "spoof" (i.e. simulate via use of an equivalent genotyping platform) a DTC-GT raw data file and upload it to the genealogy TPI tool GEDmatch. TPI tools are typically built to accept any uploaded raw data file that meets basic formatting requirements, so even if terms of use say you should not upload other people's data without their permission, there are typically no technical safeguards against it. (Notably, transferring via API does safeguard against that to some extent, in that the transferrer at least needs to have the user's 23andMe username and password to authenticate the transfer.) The implications are that if someone obtains or generates your raw data surreptitiously, they could learn about your health risks, ancestry, and relatives and — and given enough publicly available demographic data — ultimately determine your identity and match your DNA to that of a crime scene sample. According to the Erlich et al. analysis, this possibility already exists for 60% of U.S. persons with European ancestry, given the

coverage of consumer genetics and third-party databases. Their proposed solution is for DTC-GT companies to cryptographically sign the raw data file such that before it can be uploaded to a third-party site there is a digital handshake between the user, third-party site, and the DTC-GT company. This might help solve privacy issues but does not address potential harms to users who upload their own data in good faith, e.g., potential harms to consumers from false positives.

Both of these potential solutions fall short in my opinion because they simply shift the role of gatekeeper. 23andMe becomes a partial gatekeeper in deciding which TPI tools can use their API. DTC-GT companies also are gatekeepers in Erlich et al.'s proposed solution, in that companies implement and manage the cryptographic signature. We should first ask whether having a gatekeeper is the right approach before we consider who the gatekeeper(s) should be and who should hold them accountable. Restricting access to genomic information via such gatekeepers has potential drawbacks to consider. Tool developers' claims about "bridging to the literature" are to some extent true: they are making accessible information from publicly available literature and variant annotation databases. Absent a tool such as a Promethease, a user who knows about ClinVar and PubMed could undertake the same exercise, albeit with the complication of having to look up SNPs individually and matching up genotype-specific information. If access to Promethease was limited or constrained in some way (e.g., if FDA determined Promethease was a device that needed market authorization and it was forced to shut down), then should access to information sources such as ClinVar or PubMed similarly be restricted? Restricting access to these resources means removing the fruits of publicly-funded research from the public domain, which would hurt the public trust in the scientific enterprise and probably also scientists themselves by creating hurdles to access resources needed to conduct research. Notably, this consideration does not apply to tools that go beyond bridging by aggregating variants, using in-house curated literature searches, and making recommendations to users based on their genetics.

Closing off one route of access also means individuals are likely to find alternate and perhaps less reliable ways to get comparable information. This arguably happened when 23andMe stopped providing health information to new U.S. customers in late 2013, causing some to download their data and upload to Promethease. There is evidence for this trend both in my customer survey and interview results and in media reports (Regalado, 2014). In taking this path, instead of 200+ health reports from 23andMe, these users received upwards of 20,000 reports from Promethease. Furthermore, 23andMe has put significant effort into crafting reports and creating effective visualizations of genetic risk, even before their reports were vetted by the FDA. Promethease developers, on the other hand, have not had the intention to package results in this way, nor have they had the time, funding, and person power to build such a system. Rather than focusing on restricting information, instead I propose building up more robust infrastructures for delivering that information and better resources for education and engagement with consumers/users/patients. My recommendations in this regard are as follows:

1) **TPI tools** should be more transparent about who makes them, why, and using what source information. This information should be clearly and obviously stated on tool websites and in white papers. Some tools already do a fair job of this, but my experience collecting information for chapter 1 revealed that often this information is often partially if not completely obscured. (For example, for some tools finding the individual(s) responsible for tool development and/or upkeep involved researching website domain name registration and LinkedIn profiles.)
2) **DTC-GT companies** should be more explicit in endorsing or disavowing some tools. 23andMe is doing this implicitly via their API policy change, but do not seem to be going so far as to publish a list of tools with their recommendations. I suspect companies do not do this because third-party tools are competitors, and they also do not want to be seen as complicit in any harms that might occur via downstream TPI of customer data. But blanket statements by DTC-GT

companies that users should attempt to vet these TPI tools on their own does very little to materially help those users.

3) **DTC-GT companies** should also review quality control practices for the full complement of genetic data that they make available to their customers. Any measures that can be taken to reduce genotyping error rates and to identify and correct (or, at minimum, set to missing) miscalled genotypes would help reduce the burden of false positives and false negatives on customers who take their raw data into TPI systems. 23andMe, for example, uses heightened scrutiny on the subset of variants that contribute to interpreted reports, as stated on the company website (23andMe, 2017a) and indicated by FDA authorization of genetic health risk reports (FDA, 2017e). 23andMe could consider the feasibility of extending this heightened scrutiny, or some version thereof, to the full set of raw data.
4) **Variant annotation databases** should continue efforts to improve the quality of information and the diversity of genetic backgrounds represented. Indeed, the interpretive engines on which most TPI tools run (e.g., ClinVar, GWAS Catalog, etc.) are the same tools used by genetics researchers and providers. Therefore, attempts to improve the quality and representativeness of information in these annotation databases would benefit both the professional genetics community and the users and developers of TPI tools.
5) **Health care providers** should be willing to talk with their patients about their genetic data and TPI reports. While potentially unpopular, this recommendation is in line with other calls to increase genetics training among non-genetics health care providers (Baars et al., 2005; Burke, 2004). While we might focus on how many people *do* bring their DTC-GT or TPI reports, we might instead ask why more people do *not*. Is it really preferable to have individuals process this information on their own and potentially make their own decisions regarding changes in health behaviors, supplementation, and/or medication?

6) **Genetics providers**, including medical genetics and genetics counseling clinics, should post educational material about DTC-GT and TPI tools on publicly-available clinic websites. Some clinics have either unwritten or codified policies to not see patients who want to discuss these reports. This is understandable given the limited number of genetics providers and the desire to focus on more urgent patient situations. However, it might actually save these clinics triage time if they could point prospective patients to online information that would help them better understand and process their TPI reports — including determining when there is actually a positive underlying family history that might merit a clinic visit.
7) Finally, the **larger community of genetics professionals** (researchers and providers) and the agencies that fund them (e.g., National Institutes of Health, Centers for Disease Control Office of Public Health Genomics) should take a more proactive role in educating and engaging with the public on these issues. There is a great opportunity to harness and cultivate the public's enthusiasm and hunger for personal genetic information. Specifically, the professional genetics community could provide engaging educational materials on the risks and benefits of analyzing raw data via TPI, perhaps centrally hosted on funding agency websites. Some attempts like this have been made for DTC-GT testing, but they seem to be out of date and not easily findable.

Future research

There are several directions in which future research could build upon and extend the knowledge I have generated in this project. First, my study of TPI tools was cross-sectional in that it examined the existing tools I was aware of at the time of study (mid to late 2016). Additional tools have since and continue to become available, which could be integrated into an expanded content analysis. Alongside the growing TPI market is continued expansion and diversification of the DTC-GT industry, including increased availability of whole-genome sequencing DTC (Begley, 2018) that could contribute to

more and more diverse use of TPI. In addition, while my use of a convenience sample of DTC-GT customers yielded abundant reports of TPI tool usage, future research could conduct a similar survey in a representative sample of DTC-GT customers. Though it could be difficult to define a representative sample in such a rapidly expanding market (e.g., see industry growth as reported by Regalado, 2018). Furthermore, other stakeholder groups in addition to tool developers, DTC-GT customers/tool users, and policymakers should be considered. In particular, further research is needed on the perspectives and experiences of health care providers, to whom TPI tool users may bring their reports. Allen et al. (2018) have studied genetic counselors in this regard; however, results from my survey and the one prior survey (Wang et al., 2018) indicate that the majority of tool users bring their TPI reports to general practitioners or non-genetics specialists. Future studies should therefore include these provider types.

Alternative routes to access raw data beyond DTC-GT, such as clinical genome sequencing or research participation, also merit further study to understand whether and how uses of raw data and TPI may differ in these contexts. Notably, return of raw data to participants in the "All of Us" 1-million-person cohort (Karow, 2018) would offer an incredible opportunity to study potential use of raw data by research participants on a large scale. In the clinical context, I am not aware of any systematic study of patients exercising their HIPAA direct access right to access uninterpreted data from clinical genome sequencing. Clinical anecdotes or case studies may become available; however, it would be valuable to know how often the direct access right leads to raw sequence data being transferred to patients and families and whether or not they pursue further analysis via TPI tools.

Finally, my mapping of the regulatory landscape for DTC-GT raw data and TPI tools in chapter 3 was limited in scope and focused on the level of U.S. federal, health-related regulation. Future analyses could incorporate other levels, including state and local within the U.S. For example, laws governing the practice of medicine vary by state (Caulfield & McGuire, 2012), which would likely have implications for whether either the provision of raw genetic data or the activities of third-party interpreters could be

considered practicing medicine and, if so, how these activities might be regulated at the level of individual states. The global policy context should also be considered, given that DTC-GT testing kits and TPI tools are both sold/made available online to an international audience of customers and users. The online-only nature of TPI makes it even less bounded by national borders compared to DTC-GT testing, which still involves the mailing of physical spit collection kits and customer biosamples. For example, the European Union's unified approach to personal data protection codified in the General Data Protection Regulation likely impacts both the operation of DTC-GT testing providers (Future of Privacy Forum, 2018) and TPI when utilized by individuals living in the European Union.

Finally, the conclusions I have drawn throughout my project and the recommendations I have offered in this concluding chapter are informed by the empirical data I have collected throughout this project, which granted are not representative of all experiences, perspectives, and stakeholders. I also recognize my positionality as a genetic researcher may lead to an underappreciation of the extant harms that genetic counselors and clinical geneticists might observe as a result of self-directed TPI. Future research should continue to build the evidence base about how individuals are using their raw data in TPI tools and with what outcomes. Additional normative work is also needed to consider the appropriate weighting of potentially conflicting moral considerations, such as promoting individual autonomy while also shielding users from harm (Childress et al., 2002; Vayena, 2015). My discussion has also focused largely on individual use; therefore, consideration of group harms and benefits also needs to be further explored.

I have taken an interdisciplinary, multi-pronged approach to gain a better understanding of the complex ecosystem of raw genetic data and TPI. I have examined in-depth the tools themselves and their developers, the tool users' motivations and practices, and finally the approaches that policymakers can take when considering potential policy responses. I have used mixed-methods approaches, gathering quantitative and qualitative data to both identify and describe trends and associations

numerically while also gaining deeper and more nuanced insights into individual experiences. I hope this work can be taken forward to inform future research in these rapidly evolving areas, to increase understanding between those whose opinions and experiences land them on opposite sides of these issues, and to assist policymakers in determining the best approaches to protect consumers while also enhancing individual autonomy and promoting interest and literacy in the fascinating field of genetics.

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APPENDIX: SURVEY INSTRUMENT

Direct-to-consumer genetic testing and "raw" genetic data: Eligibility

Informational statement

We are researchers at the University of Washington conducting a study of direct-to-consumer genetic testing and are looking for individuals who are willing to take an online survey on this topic.

You should only take this survey if you have done a direct-to-consumer genetic test and are at least 18 years old.

This survey should take approximately 15 minutes or less to complete. There are no direct benefits to you for participating. There is a chance you may find some questions frustrating or stressful. Your survey responses will be collected by a secure online survey program and stored on a password-protected computer. However, we cannot ensure the complete confidentiality of your responses, as data breaches are always possible. We will take all available measures, however, to make sure your survey responses stay safe and secure.

If you have any questions about the study, or if you feel you have been harmed by participating, you may contact the research team at sarahcn@uw.edu. If you have complaints or questions about your rights as a research participant, contact the University of Washington Human Subjects Division at (206) 543-0098. Participation is voluntary, and you may choose not to participate or to withdraw from the study at any time without penalty or loss of benefits to which you are otherwise entitled.

Please answer the questions below to determine if you are eligible for this survey study.

I am at least 18 years old.	◯ Yes ◯ No	*If "No," exit survey*
I have used a direct-consumer-genetic testing company such as 23andMe, AncestryDNA, or FamilyTreeDNA.	◯ Yes ◯ No	*If "No," exit survey*
I have read the information above and I agree to participate in this study.	◯ Yes, I wish to participate ◯ No, I do not wish to participate	*If "No," exit survey*
LOOP	◯ Facebook ◯ Twitter ◯ Open Reading Frame website ◯ Direct invite ◯ ITHS portal ◯ Craigslist ◯ Quantified Self newsletter ◯ Reddit	*Hidden variable auto-populated via recruitment venue specific URLs*

Direct-to-consumer genetic testing and "raw" genetic data

Part I: Your direct-to-consumer genetic test

Below is a list of direct-to-consumer genetic testing companies. Please check the box next to the company name if you have ordered a test from that company.

- ☐ 23andMe
- ☐ AncestryDNA
- ☐ Family Tree DNA
- ☐ Other

Specify company _____ *Displayed if "Other" selected*

Testing date questions below displayed only for the DTC companies selected on Page 2.

You answered that you have ordered a 23andMe test. To the best of your memory, please indicate the date you ordered the test.

Month:

◯ Jan ◯ Feb ◯ Mar
◯ Apr ◯ May ◯ June
◯ July ◯ Aug ◯ Sep
◯ Oct ◯ Nov ◯ Dec
(Month you ordered 23andMe test)

Year (YYYY):

_____
(Year you ordered 23andMe test)

You answered that you have ordered an AncestryDNA test. To the best of your memory, please indicate the date you ordered the test.

Month:

◯ Jan ◯ Feb ◯ Mar
◯ Apr ◯ May ◯ June
◯ July ◯ Aug ◯ Sep
◯ Oct ◯ Nov ◯ Dec
(Month you ordered AncestryDNA test)

Year (YYYY):

_____
(Year you ordered AncestryDNA test)

You answered that you have ordered a Family Tree DNA test. To the best of your memory, please indicate the date you ordered the test.

Month:

◯ Jan ◯ Feb ◯ Mar
◯ Apr ◯ May ◯ June
◯ July ◯ Aug ◯ Sep
◯ Oct ◯ Nov ◯ Dec
(Month you ordered FamilyTree DNA test)

Year (YYYY)

_____
(Year you ordered Family Tree DNA test)

You answered that you have ordered a test from [othercomp]. To the best of your memory, please indicate the date you ordered the test.

Month:

◯ Jan
◯ Feb
◯ Mar
◯ Apr
◯ May
◯ June
◯ July
◯ Aug
◯ Sep
◯ Oct
◯ Nov
◯ Dec
(Month you ordered [othercomp] test)

Year (YYYY)

_____
(Year you ordered [othercomp] test)

Displayed only when "23andMe" is selected on Page 2

You answered that you have ordered a 23andMe test. Did you receive health reports from 23andMe?

Health reports include information about genetic influences on risk for various diseases (for example: diabetes, cancer, and asthma), how you respond to different drugs (pharmacogenetics), or whether you carry genetic risk variants that when passed on by both parents can cause certain diseases in a child (carrier status). Health reports do NOT include information about physical traits such as eye color or earwax type, or wellness traits such as caffeine metabolism or lactose intolerance.

◯ Yes
◯ No
◯ Don't know

People seek direct-to-consumer genetic testing for a number of different reasons. For each of the potential reasons shown below, please rate how important the reason was in your decision to seek direct-to-consumer genetic testing.

	Very important	Somewhat important	Not at all important
General curiosity about my genetics	○	○	○
Desire to learn more about my ancestry (e.g., ethnic breakdown)	○	○	○
Desire to find relatives	○	○	○
Desire to find out about my personal risk for specific diseases	○	○	○
I have limited information about my family health history	○	○	○
Other members of my family are using personal genomic services	○	○	○
Desire to participate in genetic research	○	○	○
Desire to have my "raw" genetic data file	○	○	○

If there are any additional reasons that were important in your decision to seek direct-to-consumer testing, please describe these additional reasons below.

Part II: Your "raw" genetic data file

Direct-to-consumer genetic testing companies usually make two types of information available to customers: (1) interpreted reports - for example, about ancestry or health - and (2) an uninterpreted or "raw" genetic data file, which you must download from the company website onto your computer. In this section, we're going to ask you about that second type, your raw genetic data file.

In case you were wondering, a raw genetic data file is a long list of all the sites in your DNA tested by the company. A raw genetic data file is between half a million to a million rows, where each row shows which chemical "letter" of DNA (A, C, G, or T) you have at a particular site.

Only companies selected on Page 2 displayed:

As of today, have you downloaded your raw genetic data file from this DTC company?

	Yes	No	Unsure
23andMe	◯	◯	◯
AncestryDNA	◯	◯	◯
Family Tree DNA	◯	◯	◯
[othercomp]	◯	◯	◯

CALC_NO_DOWNLOAD _____ *Hidden variable*

Displayed only when "No" or "Unsure" is selected for one or more DTC companies on Page 6

You indicated that you have not downloaded or are unsure if you have downloaded your raw genetic data file from at least one DTC company.

For each of the following statements, please select the most appropriate response.

	Strongly Agree	Agree	Disagree	N/A
I am interested in having my raw genetic data file	○	○	○	○
Prior to taking this survey, I was aware my raw genetic data was available	○	○	○	○
I had trouble finding my raw genetic data file on the company website	○	○	○	○
I had trouble downloading my raw genetic data file from the company website	○	○	○	○
I am planning to download my raw genetic data file but have just not gotten around to it yet	○	○	○	○
The company I used does not offer a raw genetic data file for download	○	○	○	○
I already had my raw genetic data from another direct-to-consumer genetic testing company	○	○	○	○

Please describe below any additional reasons that you have not downloaded your raw genetic data file.

Please note that taking this survey is not meant to encourage you to download your raw genetic data, an option that you may have been unaware of before taking this survey.

CALC_HAS_DOWNLOADED _____ *Hidden variable*

Displayed only when "Yes" is selected for one or more DTC companies on Page 6. Those respondents only selecting "No" or "Unsure" on Page 6 progress to Page 17 (Demographics section).

Part III: Genetic data interpretation tools

You indicated that you have downloaded your "raw" genetic data file from a direct-to-consumer genetic test. There are many independent tools online where you can upload your genetic data file for further interpretation and analysis. These tools are separate from the direct-to-consumer company that provided you with your "raw" genetic data. Next we are going to ask about some of these tools. Don't worry if all or most of these tools are unfamiliar to you, just answer as best you can.

Below is a list of online interpretation tools. For each tool, please indicate whether or not you have used the tool at least once.

	Have used	Have not used
Athletigen	◯	◯
DNA Doctor	◯	◯
DNA.land	◯	◯
DNA Fit	◯	◯
GEDMatch	◯	◯
Gene Knot	◯	◯
Genetic Genie	◯	◯
Interpretome	◯	◯
Infinome	◯	◯
Livewello	◯	◯
Nutra Hacker	◯	◯
openSNP	◯	◯
Promethease	◯	◯
Other	◯	◯

What other tools have you used?

Displayed if "Other" selected

_____

CALC_NUM_TOOL _____ *Hidden variable*

Have you given your raw genetic data file to anyone else to run through a third-party interpretation tool for you?

◯ Yes
◯ No

Who did you give your raw genetic data file to? *Displayed if "Yes" selected in preceeding question*

◯ Family member
◯ Friend
◯ Other

Who else did you give your raw data file to? _____ *Displayed if "Other" selected*

If you know which third-party tool(s) this other person ran your data through for you, please indicate below.

◯ Athletigen
◯ DNA Doctor
◯ DNA.land
◯ DNA Fit
◯ GEDMatch
◯ Gene Knot
◯ Genetic Genie
◯ Interpretome
◯ Infinome
◯ Livewello
◯ Nutra Hacker
◯ openSNP
◯ Promethease
◯ Other
◯ Don't Know

Other tool name: _____ *Displayed if "Other" selected*

You indicated you have used Athletigen and no other interpretation tool. (If this is not correct, you may use the 'Previous Page' button to select additional tools.) Next we are going to ask you some questions about Athletigen.

You indicated you have used DNA Doctor and no other interpretation tool. (If this is not correct, you may use the 'Previous Page' button to select additional tools.) Next we are going to ask you some questions about DNA Doctor.

You indicated you have used DNA.land and no other interpretation tool. (If this is not correct, you may use the 'Previous Page' button to select additional tools.) Next we are going to ask you some questions about DNA.land.

You indicated you have used DNA Fit and no other interpretation tool. (If this is not correct, you may use the 'Previous Page' button to select additional tools.) Next we are going to ask you some questions about DNA Fit.

You indicated you have used GEDMatch and no other interpretation tool. (If this is not correct, you may use the 'Previous Page' button to select additional tools.) Next we are going to ask you some questions about GEDMatch.

You indicated you have used Gene Knot and no other interpretation tool. (If this is not correct, you may use the 'Previous Page' button to select additional tools.) Next we are going to ask you some questions about Gene Knot.

You indicated you have used Genetic Genie and no other interpretation tool. (If this is not correct, you may use the 'Previous Page' button to select additional tools.) Next we are going to ask you some questions about Genetic Genie.

You indicated you have used Interpretome and no other interpretation tool. (If this is not correct, you may use the 'Previous Page' button to select additional tools.) Next we are going to ask you some questions about Interpretome.

You indicated you have used Infinome and no other interpretation tool. (If this is not correct, you may use the 'Previous Page' button to select additional tools.) Next we are going to ask you some questions about Infinome.

For respondents who selected "Have used" for only one tool on Page 8, the text "You Indicated you have used ___ and no other interpretation tool..." was displayed, with the appropriate tool name filled in.

You indicated you have used Livewello and no other interpretation tool. (If this is not correct, you may use the 'Previous Page' button to select additional tools.) Next we are going to ask you some questions about Livewello.

You indicated you have used Nutra Hacker and no other interpretation tool. (If this is not correct, you may use the 'Previous Page' button to select additional tools.) Next we are going to ask you some questions about Nutra Hacker.

You indicated you have used openSNP and no other interpretation tool. (If this is not correct, you may use the 'Previous Page' button to select additional tools.) Next we are going to ask you some questions about openSNP.

You indicated you have used Promethease and no other interpretation tool. (If this is not correct, you may use the 'Previous Page' button to select additional tools.) Next we are going to ask you some questions about Promethease.

You indicated you have used [othertool] and no other interpretation tool. (If this is not correct, you may use the 'Previous Page' button to select additional tools.) Next we are going to ask you some questions about [othertool].

For respondents answering "Have used" for more than one tool on Page 8, this question was displayed giving as options only the tools selected on Page 8.

Because you indicated that you have used more than one tool, please select one below on which to base your answers to the following questions. This may be the tool you have used the most, or perhaps the one you found most interesting or useful.

	Will focus on
Athletigen	◯
DNA Doctor	◯
DNA.land	◯
DNA Fit	◯
GEDMatch	◯
Gene Knot	◯
Genetic Genie	◯
Interpretome	◯
Infinome	◯
Livewello	◯
Nutra Hacker	◯
openSNP	◯
Promethease	◯
[othertool]	◯

Of the following reasons, which best describes why you selected this tool in the previous question?

◯ Compared to the other tool(s) I've used, this was my favorite
◯ Compared to the other tool(s) I've used, this was my least favorite
◯ Compared to the other tool(s) I've used, I have used this one the most frequently
◯ Compared to the other tool(s) I've used, I have used this one the most recently
◯ Other

Please describe the other reason: *Displayed if "Other" selected*

When was the last time you used this tool?

◯ In the past week
◯ In the past month
◯ In the past year
◯ In the past five years

Based on your use of this tool, please rate the accuracy of the following statements

	Strongly Agree	Agree	Disagree	Strongly Disagree
I received information about my health	◯	◯	◯	◯
I received information about my risk of specific diseases	◯	◯	◯	◯
I received information about my ancestry (e.g., ethnic breakdown)	◯	◯	◯	◯
I received information about family members/relatives	◯	◯	◯	◯
I got a better understanding of genetics in general	◯	◯	◯	◯
I got a better understanding of how direct-to-consumer genetic testing companies interpret genetic data	◯	◯	◯	◯

How did you learn about the tool? Please select all that apply.

- ☐ Friend or family member
- ☐ Online search engine (e.g., Google)
- ☐ DTC company customer forums
- ☐ Social media
- ☐ News articles
- ☐ Other online sources (blogs, wikipedia, etc.)
- ☐ Television
- ☐ Other

Please specify: _____ *Dispayed if "Other" selected*

Displayed if "Social media" was selected above

From which of the following social media platforms did you learn about the tool? Please select all that apply.

- ☐ Facebook
- ☐ Twitter
- ☐ Reddit
- ☐ Tumblr
- ☐ Instagram
- ☐ YouTube
- ☐ Other

Please specify: _____ *Displayed if "Other" selected*

Did you take any of the following actions in response to information you got from the tool?

	Yes	No
Shared the information with a health care provider	○	○
Shared the information with a family member	○	○
Shared the information with a non-family member friend or loved one	○	○
Pursued analysis with a different interpretation tool	○	○
Pursued more genetic testing	○	○
Participated in a genetic research study	○	○
Made changes to my health insurance	○	○
Made changes to my life insurance or long-term care insurance	○	○

Displayed if answer was "Yes" to "Shared the information with a health care provider" on Page 12

You indicated you shared the information from the tool with a health care provider. Please indicate below what type(s) of health care provider you discussed the information with.

	Yes	No
General practitioner	◯	◯
Medical geneticist	◯	◯
Genetic counselor	◯	◯
Other health care provider	◯	◯

What other type of health care provider did you discuss the results with?

Displayed if answer was "Yes" to "Other health care provider"

_____

If there are other actions you took in response to information you got from using the tool, please describe these below.

Based on your use of this tool, please rate the accuracy of the following statements

	Strongly Agree	Agree	Disagree	Strongly Disagree
I felt confused by the information I received	○	○	○	○
I felt satisfied with the information I received	○	○	○	○
I felt upset by the information I received	○	○	○	○
I was glad I chose to use this tool	○	○	○	○

When choosing to use the tool, how important to you were the following features?

	Very important	Somewhat important	Not at all important
Access to health information	◯	◯	◯
Access to information about my ancestry (e.g., ethnic breakdown)	◯	◯	◯
Ability to find relatives/family members	◯	◯	◯
Ability to contribute to research	◯	◯	◯
Privacy and security of my data	◯	◯	◯
Knowing who (e.g., individual, company) made the tool	◯	◯	◯
Trusting the individual or company who made the tool	◯	◯	◯

If there are other features important to you when choosing to use an interpretation tool, please describe these below.

Is there anything that you've wanted to do with your raw genetic data file that you haven't been able to do? If so, what else have you wanted to do and why?

Is there anything else you'd like to tell us about your experience with this or any other interpretation tool that you have tried? If so, please do so below.

What year were you born?

_____

Do you currently live in the US?

◯ Yes
◯ No

In what country do you currently live? *Intended to display when answer was "Yes" to preceeding question. However, due to branching error logic, was not displayed for any respondent.*

_____

What gender do you identify as?

◯ Man
◯ Woman
◯ Other
◯ Prefer not to answer

How do you describe your race? Check all that apply

☐ American Indian/Alaska Native
☐ Asian
☐ Black of African American
☐ Hawaiian or Pacific Islander
☐ White
☐ Other
☐ Prefer not to answer

Do you consider yourself to be Hispanic or Latino?

◯ Yes
◯ No
◯ Prefer not to answer

What is the highest level of education you have completed? If currently enrolled, highest level received.

◯ Less than high school
◯ High school graduate or GED
◯ College degree
◯ Master's degree
◯ Doctorate or other terminal degree

In which field is your current occupation (or last occupation, if unemployed or retired)?

◯ Business, Financial, Management, Sales, and Related Occupations
◯ Computer, Engineering and Mathematical Science
◯ Life, Physical, and Social Science
◯ Legal
◯ Education, Training, and Library
◯ Arts, Design, Entertainment, Sports, and Media
◯ Healthcare practitioner
◯ Office and Administrative Support
◯ Construction, Maintenance, and Natural Resources
◯ Production and Transportation
◯ Other

Please specify your occupation: *Displayed if "Other" was selected*

_____

Do you work in genetic research or genetic medicine?

◯ Yes
◯ No

Have you ever participated in a genetic research study, outside of any direct-to-consumer genetic testing company research you may have joined?

◯ Yes
◯ No
◯ Don't know

How did you hear about this survey?

◯ Twitter
◯ Facebook
◯ Craigslist
◯ ITHS Participant Portal
◯ Direct researcher contact
◯ Reddit
◯ Quantified Self Newsletter
◯ Other

What other way did you hear about this survey? _____ *Displayed if "Other" was selected*

Thank you so much for completing the survey!

Just one last question.

Are you willing to participate in a follow-up interview for this project? If so, please provide your name and contact information below. The study team may or may not contact you, depending on how many people volunteer to be contacted.

Name

_____

What is your preferred mode of contact?

◯ email
◯ phone
◯ other

What is your preferred email address?

Displayed if "email" selected above

_____

What is your preferred phone number?

Displaed if '"phone" selected above

_____

How would you like to be contacted?

Displayed if "other" selected above

_____