Evaluation of a scalable method for returning results and genetic findings from genomic research to research participants

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Introduction

The issue of returning research results and incidental findings to research participants has come to the forefront in recent years, garnering mentions in the New York Times[1] and Forbes[2], as well as significant amounts of funding from the NIH[3]. This interest is fueled in part by the increasing prevalence of genome-wide sequencing projects. While studies have shown that many research participants who have donated DNA samples to research would like to receive individual results from projects performed using their samples[4], the questions of how and when to return which findings are still hotly debated. Multiple NIH-funded working groups have published recommendations on the process of returning results, but without practical demonstrations of how the process could work, widespread implementation of such policies could remain a daunting task.

Fortunately, direct-to-consumer personal genomics companies provide a concrete, real-world testing ground for returning genetic findings to consumers. In the case of 23andMe's Personal Genome Service® (PGS®), a subset of the customers were specifically recruited to participate in research projects and may not have had an interest in broadly learning about their genetics when they became customers. For these individuals, the vast majority of the over 200 health reports (see Figure 1 for an example) provided by 23andMe would likely constitute incidental findings, as they are outside the focus of the research project. Thus, looking at the health report viewing behavior of these customers could provide a sense of how interested research participants are in learning about such incidental findings.

This analysis focuses on how well the PGS addresses working group recommendations on the return of incidental findings (health findings outside the focus of the research being conducted) and individual research results, as well as the health report viewing behavior of 23andMe customers who come to the service primarily for research versus those who come for other reasons. While issues of privacy, data security, and risk communication are also important and inform critical aspects of 23andMe's solution, they are outside the scope of this study.

Methods

Comparison of 23andMe's PGS to working group recommendations

A literature review on return of results identified two major papers providing recommendations on the topic, both written by working groups funded primarily by the NIH: Wolf et al. 2008[5] and Wolf et al. 2012[6]. The methods used by 23andMe were compared to recommendations from these reports.

Comparison of health report viewing behavior of 23andMe customers who were recruited for a research project with customers who came in for other reasons

Data was drawn from ~150,000 23andMe customers who agreed to an IRB-approved consent document. We examined whether certain groups of individuals accessed at least one of the three health reports that require explicit user action to view (as opposed to being available on a summary page). These three reports provides results on variants in the *APOE*, *LRRK2*, and *BRCA* genes. Specifically, we compared "research" customers (individuals who became customers for one of four specific research initiatives on Parkinson's disease, sarcoma, myeloproliferative neoplasms, or African ancestry) with "regular" customers (those who presumably became customers for other reasons, such as curiosity about health or ancestry).

Results

Sixteen recommendations were identified in the two Wolf et al. papers. While the 23andMe system is not perfectly analogous to the scenarios outlined by the working groups, it is still closely aligned. 23andMe has policies that address 16/16 recommendations. See Tables 1 and 2.

In Table 3, the percentage of "research" customers who viewed at least one of the Alzheimer's disease, Parkinson's disease, or breast cancer health reports is compared to the percentage of "regular" customers who did the same. Though a lower percentage of research customers opened the reports, the numbers are still high overall (68% of all research customers viewed at least one report).

Table 1. 23andMe policies address 6/6 working group recommendations (2008) for addressing incidental findings.

Working group recommendation[a]	23andMe policy
Address incidental findings in the consent process	Addressed in 23andMe Terms of Service: "You may learn information about yourself that you do not anticipate. This information may evoke strong emotions and has the potential to alter your life and worldview. You may discover things about yourself that trouble you and that you may not have the ability to control or change (e.g., your father is not genetically your father, surprising facts related to your ancestry, or that someone with your genotype may have a higher than average chance of developing a specific condition or disease). These outcomes could have social, legal, or economic implications."
Address the potential for incidental findings in future analyses of archived data	Addressed in 23andMe Terms of Service: "Future scientific research may change the interpretation of your DNA. In the future, the scientific community may show previous research to be incomplete or inaccurate."
Plan for the discovery of incidental findings	Reporting on health findings based on a customer's genetics is an integral part of the 23andMe PGS so how this is accomplished is carefully planned for and addressed by the 23andMe team.
Plan to verify and evaluate a suspected incidental finding, with an expert consultant if needed	23andMe's genetic association vetting process is designed to identify which findings are likely to be true and assign a level of confidence to each (see white paper: https://23andme.https.internapcdn.net/res/pdf/f6Jjz_mcXDI0BTfj-EA9tw_23-03_Vetting_Genetic_Associations_2011_08.pdf). External experts are brought in to consult on specific cases from time to time. For our own findings, we adhere to standards in the field for statistical significance. Findings are shared via health reports (see figure 1).
Plan to determine whether to report an incidental finding, based on likely health or reproductive importance	23andMe believes that the participant can decide which information they are likely to find beneficial. 23andMe judges a finding primarily on its analytical validity and the strength of the association, not on the nature of the data. A participant can choose to learn about his or her risk for conditions ranging from Alzheimer's disease to breast cancer to lactose tolerance to freckling.
Investigators and IRBs should create and monitor a pathway for incidental findings	See above for discussion of vetting process.

[a] Recommendations from Wolf et al. 2008[5] which focuses on managing incidental findings from human subjects research (not specific to genetic research).

Table 2. 23andMe policies address 10/10 working group recommendations (2012) for addressing incidental findings and research results.

Working group recommendation[a]	23andMe policy
A biobank should take responsibility to make sure biobank system players fulfill incidental finding and individual research results responsibilities	23andMe ensures that new findings are returned to participants through the PGS.
Biobanks should develop an explicit policy on whether incidental findings and individual research results will be returned	23andMe strongly believes in providing individuals with as much quality genetic information as possible (see 23andMe core values at https://www.23andme.com/about/values/) and in getting results from participating in research (https://customercare.23andme.com/entries/21259407-what-do-i-get-in-return-for-taking-surveys).
Biobanks should have a multidisciplinary committee for clarifying criteria on what data to return, analyzing a finding to determine whether it should be returned, reidentifying appropriate contributors, and recontacting contributors to offer new findings	All of 23andMe's processes on what data to return, how it should be presented, and how to contact participants are developed by an internal, multidisciplinary team with scientific, medical, legal, and product design expertise (see above for discussion of vetting process).
Biobanks should work with researchers to determine which findings should be returned	23andMe has specific guidelines on how to vet which data is returned to participants, as described in our white paper (link in Table 1). These guidelines are continuously evaluated in conjunction with our scientific advisory board.
Biobanks should take primary responsibility for analyzing findings except when the finding is a result of the primary researcher's research	23andMe has developed a rigorous method (see link for white paper in Table 1) for determining whether a finding (either from 23andMe research or from the literature) should be presented to participants. All our genetic data is obtained from a CLIA-certified lab.
Researchers and biobanks should decide ahead of time how to handle re-identification of contributors	23andMe researchers do not have access to contact information to protect participant privacy, but 23andMe does maintain active contact with its participants as part of its online service. As a result, participants can be reidentified and recontacted on an as-needed basis.
Researchers and biobanks should decide ahead of time how to recontact contributors. Findings should be returned in a form that is understandable to the contributor and his/her clinician	23andMe recontacts all research participants by email and through their online 23andMe accounts. An entire team of scientists, product designers, and engineers is devoted to providing findings to participants in a form that is understandable to non-scientists.
Biobanks should engage with contributors to determine their preferences and priorities for return of findings	23andMe conducts both quantitative and qualitative user experience research to understand how customers understand the reports describing their genetic data and how they would like their results to be organized and displayed.
Researchers should publish aggregated results in scholarly journals and communicate results to contributors as well	23andMe has published nine open-access papers in scholarly journals on findings made in the 23andMe database. Each paper has been accompanied by a blog post on the 23andMe blog describing the results of the study in lay language. Some findings are also translated into reports in the PGS so that participants can see how findings map onto their own genetic data.
Funders and regulators should make sure that researchers and biobanks have adequate funding to support responsible return of incidental findings and individual research results	Currently 23andMe is the main funder of its research, and as part of that program, has implemented a method to support responsible return of incidental and research findings that updates research participants on the meaning of their genetic data as new findings are released. It is likely to be more resource-efficient for other researchers to capitalize on the large investment already made by 23andMe.

[a]Recommendations from Wolf et al. 2012[6] which focuses on managing both incidental findings and individual of research results in biobank systems. Note that in this scenario, 23andMe is both "biobank" and "researcher".

Table 3. Almost 70% of research customers chose to view at least one health report

Group[a]	% viewed at least one report[b]
Sarcoma	78%
Myeloproliferative neoplasms	83%
Parkinson's disease	47%
African ancestry	80%
ALL RESEARCH CUSTOMERS	**68%**
REGULAR CUSTOMERS	**86%**

[a]For definitions of groups, see Methods. [b]Percentage of different groups of customers who have viewed at least one of the Alzheimer's disease, Parkinson's disease, or breast cancer reports.

Discussion

While the issue of how to return incidental findings and research results in genomics research will rightly continue to be the subject of much discussion, this work demonstrates not only that 23andMe has developed a practical and scalable solution to this challenge, but also that research participants are interested in consuming this information. With the lessons learned from the development of its PGS, 23andMe could assist other researchers with the responsible return of results.

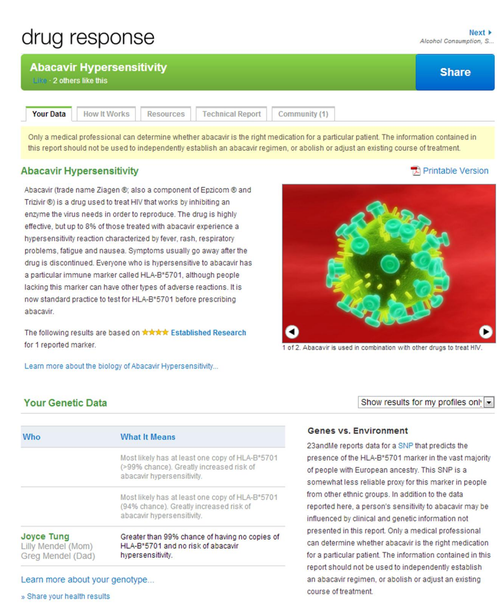

Figure 1. How findings can be presented to research participants – a sample 23andMe health report.

Acknowledgments

We would like to thank 23andMe's customers who consented to participate in research for enabling this study. We also thank the employees of 23andMe who contributed to the development of the infrastructure that made this research possible.

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