Genetics patients' perspectives on clinical genomic testing

Aims: Advances in next-generation sequencing technologies make it possible to envisage multiple contexts in which genomic tools might be used to enhance patient care. We describe how genetics patients and their caregivers view the promises and perils of clinical genomic testing. **Patients & methods:** Fifty-one interviews with patients and parents of pediatric patients seeking genetic evaluation at an academic medical center. **Results:** Themes from interviews include participants' enthusiasm for clinical genomic testing for diagnostic purposes, medical benefits and concerns about emotional and psychosocial burdens resulting from clinical genomic testing. **Conclusion:** By clarifying these patients' and caregivers' views of clinical genomic testing, the findings we report can help to anticipate other patients' reactions to new forms of personalized medicine enabled by genomic technologies.

KEYWORDS: clinical genomic testing ▪ genetics patient ▪ next-generation sequencing ▪ patient attitudes ▪ qualitative research

Michelle L McGowan[1,2], Allison Glinka[3], Janelle Highland[4], George Asaad[5] & Richard R Sharp*[2,4,6]

[1]Department of Bioethics, Case Western Reserve University, Cleveland, OH, USA
[2]Center for Genetic Research Ethics & Law, Case Western Reserve University, Cleveland, OH, USA
[3]University of Toledo Medical Center, Toledo, OH, USA
[4]Department of Bioethics, Cleveland Clinic, Cleveland, OH, USA
[5]Ohio University College of Osteopathic Medicine, Athens, OH, USA
[6]Genomic Medicine Institute, Cleveland Clinic, Cleveland, OH, USA
**Author for correspondence: Tel.: +1 216 445 1257 sharpr3@ccf.org*

Rapid advances in next-generation sequencing (NGS) technologies have generated great interest in clinical applications of genome-wide analyses [1–3]. Although much of this excitement has focused on the prospect of using NGS to assess an individual's likelihood of developing various diseases over their lifetime and ability to metabolize specific drugs (i.e., personalized medicine and pharmacogenomics), to date, the most compelling illustrations of the power of NGS have been in more conventional genetic-testing settings. For example, Lupski and colleagues recently showed how whole-genome sequencing could be used to identify novel genetic contributions to disease [4]. Similarly, Worthey and colleagues have shown how whole-exome sequencing might be used to diagnose disease in patients for whom a genetic diagnosis has been elusive [5].

These early demonstrations of the clinical promise of genomic analyses suggest that NGS tools will be adopted first by physicians who are consulted to assist in providing a diagnosis for patients with complex clinical presentations, particularly in cases where genetic contributions are suspected but have proven difficult to identify [6]. Examples of such scenarios might include patients presenting with neurological problems of unknown origins or with complex cancer histories that are suggestive of multiple genetic contributions [7].

There has been increasing recognition in the medical and bioethics literature that clinical genomic testing will require a departure from existing standards of care in medical genetics due to the uncertain significance of results, the volume of data produced and the dynamic nature of knowledge generated through genomic science [8,9]. To the extent that early experiences with clinical genomic testing will play an important role in the emergence of other forms of personalized genomic medicine, it is important to consider the ethical and social challenges that must be successfully navigated in this context [10].

Previous empirical research on public attitudes towards genomic testing has largely focused on the experiences of consumers of commercial genomic risk assessment products [11,12] and public opinions on new technologies [13]. Little is known about how patients, particularly patients for whom clinical applications of genomic testing may be appropriate, perceive the use of whole-exome and whole-genome sequencing for diagnostic and risk assessment purposes. Mayer and colleagues have argued that it is likely that genomic technologies will be initially introduced to patients who are already considering some type of genetic evaluation for an undiagnosed condition and that their responses to these technologies will play a key role in future developments in personalized medicine [14]. Understanding these patients' perspectives on clinical genomic testing can lay the foundation for integrating genomic technologies into patient care in the future [15].

In this paper we describe the understandings and expectations of genetics patients and their caregivers regarding the promises and perils of clinical genomic testing. As likely first users of

Future Medicine part of fsg

diagnostic tools enabled by NGS technologies, characterizing the views of these patients can provide important insights into the ethical and practical challenges associated with new forms of personalized medicine.

Patients & methods

Study design & sample

To characterize the attitudes and beliefs of patients regarding the diagnostic possibilities of genomic analysis and the types of results that should be returned following testing, we conducted semi-structured interviews with patients, their partners and parents of minor patients at three genetics clinics at the Cleveland Clinic medical center (OH, USA). Semi-structured interviews were utilized to elicit specific information from the respondents regarding clinical genomic testing. We used a set of flexibly ordered questions to allow the interviewers to respond to participants' remarks and ideas at appropriate points throughout the conversation [16]. Eligibility criteria for participation in the study included patients over 21 years of age or parents of patients younger than this, also over 21 years of age, who spoke English, who had presented for clinical genetic testing, and had not yet received results from genetic testing or received a diagnosis of a specific genetic condition. We hypothesized that this patient population may be appropriate candidates for clinical genomic testing in the future and would likely be offered forms of genomic testing (as an alternative or supplement to more conventional forms of genetic testing).

Subject recruitment

The research protocol and all study materials were approved by the Cleveland Clinic Foundation Institutional Review Board. The research team recruited individuals and couples to participate in the study using two methods: through introduction to the study by patients' healthcare providers and through direct mailing to patients and the parents of patients who had upcoming appointments at the genetics clinic. With the first approach, genetic counselors and physicians notified patients who met the eligibility criteria of the study during their appointments. Forty-five individuals expressed interest and were referred to the study team to learn more about participation in the study following their appointment with a genetic specialist, but before receiving results from genetic testing. Forty-four of these individuals provided consent and participated in the study. With the second approach, the research team sent 80 recruitment letters to the households of eligible individuals with upcoming clinic appointments. Representatives from eleven households contacted a member of the research team to schedule an interview and ten of these subsequently participated in the study, along with an additional two individuals from these households, bringing the total number of individuals recruited using this method to twelve.

Data collection

Data collection took place from January to December 2009. Written informed consent was obtained from all participants prior to interviews. At the outset of each interview, participants were given a basic description of clinical genomic testing (**Box 1**). No additional educational materials on genetic testing were provided to participants, although participants may have received genetic counseling from their clinicians prior to participating in the interview. Following this introduction, the interviewer elicited participant opinions on clinical genomic testing, including:

- General interest in genomic testing;
- Preferences regarding test administration and return of test results;
- Perceived benefits and concerns about testing;
- Sharing of test results with others.

Subjects received a US$50 gift certificate for their participation. Final sample size was determined by evaluation of theoretical saturation [17].

Data management & analysis

All interviews were audio recorded and transcribed for thematic analysis [18]. Transcripts and field notes were de-identified through the replacement of personal identifiers with ID numbers. In an iterative process combining inductive and deductive methods, the research team used their field notes and a subset of transcripts to generate a thematic summary and coding scheme [16]. To enhance intercoder reliability, a codebook including definitions and examples for each code, and rules for code application was devised [19]. Using this codebook, all transcripts were double coded by two team members and reviewed for reliability using qualitative analysis software (NVivo 8; QSR, MA, USA). Data analysts used the coding comparison query provided in NVivo to identify areas of disagreement, which were then reviewed to achieve consensus. Thematic analysis presented here is limited to descriptive and

Box 1. Description of clinical genomic testing provided to participants.

Instead of looking at a single gene responsible for one genetic disorder, this testing looks at thousands of individual changes – commonly called gene variants – in a person's DNA sequence. Looking at thousands of known DNA sequence variations will reveal risk and disease information about hundreds of conditions. The results of this testing will create a genomic risk report which includes information about your risks for health conditions and susceptibility to disease and drug-related complications.

Clinical genomic testing involves several steps:

- Meeting/evaluation with a clinical geneticist and genetic counselling;
- Obtaining a blood sample;
- Reviewing results of testing with a clinical geneticist;
- Follow-up with genetic counseling.

Generally, the time to complete all steps of this process is approximately 1 month.

analytic examination of participants' opinions on clinical genomic testing, including: general interest in genomic testing and perceived benefits and concerns regarding testing.

Results

Sixty-six individuals participated in 51 interviews for this study. Three overarching themes emerged from interviews pertaining to participants' enthusiasm for testing for diagnostic purposes; potential medical and psychosocial benefits for specific patient populations; and concerns related to emotional and psychosocial burdens that genomic risk information could pose to themselves and others, including the volume of information that would be included in clinical genomic test results. We present these major findings in greater detail below.

Demographics

Participant demographics are presented in Table 1. Interviews were conducted with individual adult patients (29), adult patients and their partners (13 interviews with 26 participants) and one or both parents of pediatric patients (9 interviews with 11 participants) for a total of 66 participants. Interviews with parents did not include their children. The 51 clinical cases represented in the sample were recruited from an adult genetics clinic (30), a cancer genetics clinic (12) and a pediatric genetics clinic (9). Participant ages ranged from 23 to 71 years. The proportion of female and male participants was 59 and 41%, respectively. Although the racial and ethnic characteristics of the study population did not differ significantly from US Census Bureau estimates for the county in which the study was conducted [101], subjects tended to be more highly educated than is typical for the area [102], with 67% having at least some college education. Just over 30% of participants reported that they were familiar with genetic conditions in their family.

Patient interest in genomic testing

Participants were receptive to the possibility of using clinical genomic testing but tempered in their enthusiasm for this approach. This enthusiasm appeared to increase as they discussed the types of findings that could be revealed through genomic evaluation with the interviewer. More than half indicated that they were more interested in clinical genomic testing at the end of the interview than they had been when introduced to this form of testing at the beginning of the interview.

Participants were considerably more interested in the use of genomic testing for diagnostic purposes than its use as a presymptomatic risk assessment tool. This likely reflects the fact that many of these participants were pursuing some form of genetic testing in response to particular symptoms that they or their children were experiencing. Participants felt that clinical genomic testing would be particularly useful for children in light of its potential to reduce the number of blood draws and clinic visits required for diagnostic evaluation. When absent of current symptoms or maladies, however, participants' interest in genomic testing was low. Illustrating this tension, a patient being evaluated for a connective tissue disorder explained:

> *"Well, I don't think anyone would want to know…I mean, it's not something you would sign up and say 'please tell me', but you start having symptoms, you want to know why. Why is this happening? So if you had something, symptoms, ok do the test and just tell me what's going on."*

In most cases, participants' interest in clinical genomic testing was based on an accurate understanding of several key features of genomic evaluation. Participants tended to characterize genomic testing as a comprehensive evaluation of their genetic disease risks. For example, an adult

Table 1. Characteristics of 66 study participants pursuing genetic testing for themselves or a family member.

Characteristic	Frequency (%)
Sex	
Male	39 (59)
Female	27 (41)
Age	
Mean age (years)	42.5
Education	
High school degree	10 (15)
Technical College Certificate	12 (18)
Some college	12 (18)
College degree	18 (27)
Graduate degree	14 (21)
Race & ethnicity	
White/Caucasian	62 (94)
Black/African–American	2 (3)
Latino	2 (3)
Familiarity with genetic conditions	
Yes	21 (32)
No	45 (68)
Interviews	
Participants	66
Interview type	
Adult genetics patient	29 (57)
Adult genetics patient and partner	13 (25)
Individual parent of pediatric genetics patient	7 (14)
Both parents of pediatric genetics patient	2 (4)
Number of patients represented in sample	51

patient described genomic testing as comparable to a "genetic whole-body scan" and a cancer genetics patient characterized it as a "blueprint for each person's genetic makeup." Participants also understood that genomic test results would be considerably more detailed than conventional laboratory tests. In addition, participants understood that genomic testing would produce estimates of disease risks, including risks for both genetic and nongenetic diseases. For instance, the wife of a patient being assessed for a connective tissue disorder explained:

"Just because you say 'Yeah, it looks like you might be susceptible to all these genetically,' that doesn't mean for sure, at least what we know now, or possibly even with the soon-to-be-released test, that it's a guaranteed thing. Nothing's really guaranteed until it happens."

Benefits of clinical genomic testing

Participants understood the benefits of clinical genomic testing in both psychosocial and medical terms. Psychosocial benefits included the belief that having access to more comprehensive information on one's genetic health risks was better than having less knowledge, knowing one's genetic health risks would improve one's quality of life or bring peace of mind, having testing would facilitate planning and decision-making for future healthcare, and getting test results could facilitate communication between family members about shared disease risks.

The following patient's characterization of the psychosocial benefit of genomic testing was typical of many:

"I think knowing something is so much better than not knowing…then at least you can plan for something you know."

Further illuminating the perceived benefit of the information provided in a genomic risk assessment for understanding and planning for one's future healthcare needs, an adult patient explained:

"I just like the idea of knowing everything. I mean, if I know the lay of the land, I have a better sense of what's next, what to do, and I think that there's a lot of cross-currents in your healthcare anyway, you know, but what's seen, what looks like the cause, may only be the major factor, but you can have a whole series of minor factors that really do complicate things…"

Other participants, such as this mother of a pediatric patient, characterized the benefit of clinical genomic testing in relation to resolving an undiagnosed genetic condition:

"I also look at the people that have children that they go years and years wondering, knowing as a mother that something isn't quite right with your child, and maybe finally finding out what that is, and just knowing so that you can treat it in a better way than not knowing, and just spending years and years, and how much money testing, trying to figure something out. You can actually target all your efforts towards that one diagnosis once you really kind of know."

Along the same lines, genomic testing was viewed as preferable to tests that assess a single gene. As another patient explained his desire for genomic testing over traditional genetic testing:

"You want to know what's going on with yourself, with your body. It seems like one test will actually look deeper into what's going on within your body than the other test. So if…I want to know what's going on with my body and everything that they can find in my body, if one test can go deeper…and finding about Crohn's Disease and you know Alzheimer's and this all in one test, then absolutely."

Many participants felt that a genomic evaluation of their disease risks could be a useful repository of information to be referenced over time for diagnoses and to expedite focused treatment for conditions that had previously been undiagnosed. An advisor to a patient in an adult genetics clinic described the long-term benefits of genomic test results:

"[These results would be] great to have because when you do have something, you go to the doctor. They're not sure what it is. They can look at your genetic record and be like 'Oh, well maybe we should run this other test because he was genetically disposed to a higher risk of x, y, z' that you wouldn't have known otherwise without… having those tests on record."

Concerns regarding clinical genomic testing

While many of these participants expressed considerable enthusiasm for the prospect of clinical genomic testing, some were more ambivalent about these benefits and also voiced a number of concerns. These concerns included emotional and psychosocial burdens that genomic risk information could pose to themselves and others, concerns about genetic discrimination, and worries about genetic privacy. One mother of a pediatric patients simulatenously voiced a benefit and such a concern:

"It would be good in the fact that there may be things that you could do to help prevent it in the long term. The bad side would be that you are constantly thinking about it and worrying about 'Am I going to develop this? Am I going to get this?'"

Some participants expressed concerns that the testing process and volume of information produced by a genomic test might be overwhelming and worried that learning their test results could have a profound impact on how they viewed themselves and their opportunities for the future. Of particular concern were findings about risk susceptibility for incurable diseases and how this information might impact one's self-perception, such as the worries voiced by a mother of a child seen in a pediatric genetics clinic:

"In looking for one thing, you find another. In this case you could potentially find many other things, many of them in mental health, many of them incurable…So in your search for one thing, you may find other things and that could be very difficult for some people really to handle, and that would be the biggest concern. You know a lot of times your patient is real focused on, they come to you for one thing and, you know, a lot of people don't want to know that they are at high risk for Alzheimer's late in life. It's going to freak them out the whole rest of their lives."

Other participants expressed concern that genomic testing might discourage vigilance with regard to health behaviors, such as the father of a child seen in a pediatric genetics clinic:

"If you've got a clean bill of health, you're not predisposed for anything and then it's like 'well, I can pretty much go out and do anything I want,' you know, and eat anything I want. So it may give people a false sense of security or, you know, just how can you still end up with heart disease if you're not predisposed, or can you still end up with cancer?"

In addition to these and other personal concerns, some participants voiced concerns that the results might be burdensome for other family members who may worry about the patient or have concerns about whether they themselves may share some of the inherited risks identified. For example, some participants felt that the uncertainty of genomic results could be harmful to their family members. As an adult patient articulated this concern:

"I wouldn't want to unduly stress out or worry family members over something that perhaps is not that …strongly correlated and, you know, cause that kind of concern over something that may not be set in stone in a concrete diagnosis."

Participants expressed worries about insurers or employers having access to genomic test results and being denied insurance coverage or employment opportunities as a result. Although less common, some patients cited concerns regarding social stigma or "genome

racism" as factors that would limit their interest in genomic testing. As the wife of a patient being evaluated for a connective tissue disorder explained:

> *"I would be very concerned about the consequences, my own personal consequences in the insurance world, business world. I don't mean personal consequences of me mentally knowing and my family knowing. It's more I'd be very worried about the medical profession sharing that information and it being out there."*

Discussion

Clinical applications of genomic technologies raise multiple practical challenges [5]. These include challenges relating to obtaining meaningful patient consent for testing, establishing realistic patient expectations and communicating very large amounts of medical information to patients in a way that they can readily understand [10,20,21]. Currently, very little is known about how patients who may be offered genomic testing in the future understand this new form of genetic testing and perceive its potential benefits and risks.

Results from this study provide a number of insights that allow us to begin to anticipate how patients may engage with clinical genomic testing in the future. In particular, our findings clarify genetic patients' understandings and expectations of genomic testing, and thus provide an important vantage point from which to assess the emergence of new forms of genomic medicine.

Overall, participants expressed moderate levels of enthusiasm for clinical genomic testing. Their enthusiasm was much greater for diagnostic application than for nontargeted forms of genetic risk assessment. Participants also voiced numerous concerns regarding genomic testing and the potential that genomic results could be misused. These findings suggest that patient response to new forms of clinical genomic testing may not be unreservedly positive and that many patients will have mixed opinions on the extent to which genomic testing is consistent with their personal values and goals.

Given that participants in this study had presented in a genetics clinic to meet with a genetics specialist regarding their own or their child's health, perhaps it is unsurprising that the majority of participants in this study had generally favorable attitudes toward genomic testing. Similar levels of enthusiasm for emergent forms of genomic testing have been reported in other prospective user populations [13]. However, one unique aspect of this study is that while this group of participants saw this type of testing as being useful for generating risk susceptibility information, they characterized the diagnostic potential for genomic testing as more valuable than predictive information about disease risks. This is a departure from the literature which has assessed prospective and actual user perspectives on commercial genomic testing platforms [11,12,22] and participants in personalized genomic research [23]. Participants in this study were especially enthusiastic about the potential for clinical genomic testing to help end a "diagnostic odyssey" and about its potential applications for children. These findings suggest that parents of children being seen by a medical geneticist may be especially receptive to new forms of genomic evaluation. This enthusiasm may be cause for concern, however, since Gahl and colleagues have noted that genomic testing may not be able to meet many patients' expectations or resolve their diagnostic uncertainties [7].

Another area where patients' and clinicians' perceptions of the value of clinical genomic testing may vary is in the desire for information. Participants in this study tended to be enthusiastic about the potential to glean information about their own personal genomic profile, even if the information may not be immediately relevant to their healthcare. This desire for more information may reflect a desire to assert control over one's own current and future health. This desire for greater amounts of information may be out of step with clinicians' judgments of the use of medical actionability as a guide for determining which genomic test results to return to patients [24,25]. Our findings highlight the potential for patients and clinicians to have very different understandings of which test results to return and potentially divergent expectations of what can be learned from clinical genomic testing.

Many of the concerns regarding genomic testing voiced by genetic patients related to the volume of information that this type of testing would produce. Some participants highlighted the potential for test results to be overwhelming and emotionally taxing for themselves and their families, which reflects similar concerns that have been raised in the literature on commercial genomic testing and whole-genome sequencing for research purposes [20,22,26]. However, insights from research involving

Alzheimer's disease patients and their families has shown that knowing one's genetic susceptibility for Alzheimer's disease allows individuals to plan for their futures [27] and that even in the face of receiving difficult information about one's disease risks, individuals exhibit emotional resilience [28,29]. So it remains to be seen how patients who pursue clinical genomic testing will react to the results they receive.

A concerning result from our study was the finding that participants tended to characterize clinical genomic testing as a comprehensive evaluation of their genetic disease risks. This suggests that patients presented with genomic testing may overestimate the scientific stability of genomic information and have a tendency to overstate the medical significance of these results. These findings also raise concerns regarding the potential for unrealistic expectations amongst patients offered clinical genomic testing. The remarkable variability of genetics patients' understandings of the promises and pitfalls of clinical genomic testing also points to a need for robust genetic education and counseling services for patients presented with the option of clinical genomic testing in the future. Future research should examine how best to return results to patients and set appropriate expectations for clinical genomic testing.

Limitations

There are several limitations associated with this study. This study reports on a small set of qualitative interviews conducted with a predominantly Caucasian, generally well-educated population receiving care at a large academic medical center in the USA. Some of our findings may be context-specific and may not be representative of genetics patients' perspectives in other healthcare settings. In addition, because clinical genomic testing has not been used widely to date, participants may have had limited familiarity genomic testing. As a result, some participants may not have clearly distinguished between genetic and genomic testing approaches.

Conclusion

Previous research on public attitudes about genomic testing has been criticized for its potential to overestimate enthusiasm for these types of tests amongst the general public [30,31]. To assess future patient responses to genomic testing, it is important to examine perspectives on genomic testing in specific patient populations that are likely to be first users of these testing options. Although the current study is limited by its focus on patients at a single academic medical center, since very few patients are currently pursuing clinical genomic testing, assessing the perspectives of this patient population can provide important insights into future responses to new forms of genomic testing.

Additionally, given that participants in this study were already pursuing genetic testing as a result of a family history or clinical

Executive summary

Background

- Genetics patients are likely to be among the first patients to be offered genomic testing for diagnostic and risk assessment purposes.
- Characterizing the perspectives of these patients can provide insights for clinicians seeking to integrate genomic testing into their practices.

Results

- Our results reveal highly variable responses to clinical genomic testing among genetics patients and moderate levels of enthusiasm for this new form of testing.
- Results from this study suggest that clinical genomic testing may be greeted by patients both with optimism about its potential to resolve diagnostic uncertainties and concerns about its potential to create unwelcome data about future disease risks.

Discussion

- Findings from this study suggest that genetic patients are most supportive of diagnostic applications of genomic testing and that these patients are less interested in receiving predictive information about disease risks.
- Genetic patients have multiple concerns regarding clinical genomic testing that clinicians should anticipate as they introduce these testing options, including concerns regarding the volume of results produced, the psychosocial burdens of learning a multitude of disease risks and the potential misuse of genomic information by others.
- Findings from this study highlight a need for robust genetics education and counseling services for those patients for whom clinical genomic testing may be appropriate.
- Additional research is needed to assess the perspectives of early adopters of clinical genomic testing, whose experiences will play an important role in the emergence of personalized medicine.

presentation that was highly suggestive of genetic disease, these patients were uniquely positioned to reflect upon the personal benefits and burdens of clinical genomic testing. By positioning our study within the context of their ongoing care and other genetic testing options that these patients were actively considering, our results shed light on the ways in which future patients will engage these new diagnostic options. The views expressed by these patients thus provide important points of reference for clinicians who may be interested in adopting new forms of genomic medicine in their clinical practice.

Perhaps most surprisingly, our results reveal highly variable responses and somewhat limited enthusiasm for clinical genomic testing amongst genetics patients. These patients expressed multiple concerns regarding clinical genomic testing that clinicians should anticipate as they introduce these new testing options to their patients. Additional research is also indicated to assess the perspectives of early adopters of clinical genomic testing, whose experiences will play an important role in the emergence of personalized medicine.

Acknowledgements

The authors thank D Cho and K Snover for their assistance in preparing this manuscript.

Disclaimer

The content is solely the responsibility of the authors and does not represent the official views of the National Human Genome Research Institute or NIH.

Financial & competing interests disclosure

This research was supported by grants from the National Human Genome Research Institute, NIH (R01-HG004500 and P50-HG003390). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

References

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1 Mcguire AL, Ponder B, Stefansson K. Personalized genomic information: preparing for the future of genetic medicine. *Nat. Rev. Genet.* 11(2), 161–165 (2010).

2 Lifton RP. Individual genomes on the horizon. *N. Engl. J. Med.* 362(13), 1235–1236 (2010).

3 Samani NJ, Tomaszewski M, Schunkert H. The personal genome – the future of personalised medicine? *Lancet* 375(9725), 1497–1498 (2010).

4 Lupski JR, Reid JG, Gonzaga-Jauregui C *et al.* Whole-genome sequencing in a patient with Charcot-Marie-Tooth neuropathy. *N. Engl. J. Med.* 362(13), 1181–1191 (2010).

5 Worthey EA, Mayer AN, Syverson GD *et al.* Making a definitive diagnosis: successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease. *Genet. Med.* 13(3), 255–262 (2011).

▪ **Illustrates how whole-exome sequencing might be used to diagnose disease in patients for whom a genetic diagnosis has been elusive.**

6 Tweardy DJ, Belmont JW. "Personalizing" academic medicine: opportunities and challenges in implementing genomic profiling. *Transl. Res.* 154(6), 288–294 (2009).

▪ **Suggests that next-generation sequencing tools are likely to be adopted first by physicians who are consulted to assist in providing a diagnosis for patients with complex clinical presentations, particularly in cases where genetic contributions are suspected but have proven difficult to identify.**

7 Gahl WA, Markello TC, Toro C *et al.* The National Institutes of Health Undiagnosed Diseases Program: insights into rare diseases. *Genet. Med.* 14(1), 51–59 (2011).

▪ **A report from the NIH Undiagnosed Diseases Program regarding their implementation of genomic technologies to establish diagnoses. While they report some successful diagnoses, the authors suggest that genomic testing may not be able to meet many patients' expectations or resolve diagnostic uncertainties.**

8 Prainsack B, Reardon J, Hindmarsh R *et al.* Personal genomes: misdirected precaution. *Nature* 456(7218), 34–35 (2008).

9 Speicher MR, Geigl JB, Tomlinson IP. Effect of genome-wide association studies, direct-to-consumer genetic testing, and high-speed sequencing technologies on predictive genetic counselling for cancer risk. *Lancet Oncol.* 11(9), 890–898 (2010).

10 Sharp RR. Downsizing genomic medicine: approaching the ethical complexity of whole-genome sequencing by starting small. *Genet. Med.* 13(3), 191–194 (2011).

▪ **Argues that to the extent that early experiences with clinical genomic testing will play an important role in the emergence of other forms of personalized genomic medicine, it is important to consider the ethical and social challenges that must be successfully navigated in this context.**

11 Bloss CS, Schork NJ, Topol EJ. Effect of direct-to-consumer genomewide profiling to assess disease risk. *N. Engl. J. Med.* 364(6), 524–534 (2011).

▪ **Reports on a quantitative study of experiences of consumers of commercial genomic risk assessment products and suggests limited psychosocial, behavioral and clinical effects of these tests.**

12 McGowan ML, Fishman JR, Lambrix MA. Personal genomics and individual identities: motivations and moral imperatives of early users. *N. Genet. Soc.* 29(3), 261–290 (2010).

▪▪ **Reports on a qualitative study of early consumers' motivations and experiences with commercial genomic risk assessment products. The study focuses on users'**

evaluations of the technologies and how they incorporate genomic risk assessment results into health-related decisions and behaviors.

13 Mcguire AL, Diaz CM, Wang T, Hilsenbeck SG. Social networkers' attitudes toward direct-to-consumer personal genome testing. *Am. J. Bioethics* 9(6–7), 3–10 (2009).

14 Mayer AN, Dimmock DP, Arca MJ *et al.* A timely arrival for genomic medicine. *Genet. Med.* 13(3), 195–196 (2011).

▪ **Argues that it is likely that genomic technologies will be initially introduced to patients who are already considering some type of genetic evaluation for an undiagnosed condition and that their responses to these technologies will play a key role in future developments in personalized medicine.**

15 Foster MW, Sharp RR. Ethical issues in medical-sequencing research: implications of genotype-phenotype studies for individuals and populations. *Hum. Mol. Genet.* 15(Spec. No. 1), R45–R49 (2006).

16 Merriam SB. *Qualitative Research: A Guide to Design and Implementation*. John Wiley & Sons, CA, USA (2009).

17 Kuzel AJ. Sampling in qualitative inquiry. In: *Doing Qualitative Research (2nd Edition)*. Crabtree BF, Miller WL (Eds). CA, USA, 33–45 (1999).

18 Kondracki N, Wellman N, Amundson D. Content analysis: review of methods and their applications in nutrition education. *J. Nutr. Educ. Behav.* 34(4), 224–230 (2002).

19 Hruschka DJ, Schwartz D, St John DC *et al.* Reliability in coding open-ended data: lessons learned from HIV behavioral research. *Field Methods* 16, 3307–3331 (2004).

20 McGuire AL, Lupski JR. Personal genome research: what should the participant be told? *Trends Genet*. 26(5), 199–201 (2010).

21 Pagon RA, Pinsky L, Beahler CC. Online medical genetics resources: a US perspective. *BMJ* 322(7293), 1035–1037 (2001).

22 Rahm AK, Feigelson HS, Wagner N *et al.* Perception of direct-to-consumer genetic testing and direct-to-consumer advertising of genetic tests among members of a large managed care organization. *J. Genet. Couns.* 21(3), 448–461 (2012).

23 Gollust SE, Gordon ES, Zayac C *et al.* Motivations and perceptions of early adopters of personalized genomics: perspectives from research participants. *Public Health Genomics* 15(1), 22–30 (2012).

▪▪ **Reports on a survey of prospective participants in the Coriell Personalized Medicine Collaborative, a study of genomic risk profiling in a research context. The results focus on participants' enthusiasm for genomic risk assessment, perceptions of risks and benefits of participation in the study, and intentions to engage healthcare providers regarding the application of their results in health promotion.**

24 Deverka PA, Schully SD, Ishibe N *et al.* Stakeholder assessment of the evidence for cancer genomic tests: insights from three case studies. *Genet. Med.* 14(7), 656–662 (2012).

25 Green RC, Berg JS, Berry GT *et al.* Exploring concordance and discordance for return of incidental findings from clinical sequencing. *Genet. Med.* 14(4), 405–410 (2012).

26 Mcguire AL, Burke W. An unwelcome side effect of direct-to-consumer personal genome testing: raiding the medical commons. *J. Am. Med. Assoc.* 300(22), 2669–2671 (2008).

27 Gooding HC, Linnenbringer EL, Burack J *et al.* Genetic susceptibility testing for Alzheimer disease: motivation to obtain information and control as precursors to coping with increased risk. *Patient Educ. Couns.* 64(1–3), 259–267 (2006).

28 Cassidy MR, Roberts JS, Bird TD *et al.* Comparing test-specific distress of susceptibility versus deterministic genetic testing for Alzheimer's disease. *Alzheimers Dement*. 4(6), 406–413 (2008).

29 Chao S, Roberts JS, Marteau TM *et al.* Health behavior changes after genetic risk assessment for Alzheimer disease: the REVEAL study. *Alzheimer Dis. Assoc. Disord.* 22(1), 94–97 (2008).

30 Bunnik E, Janssens AC, Schermer M. How attitudes research contributes to overoptimistic expectations of personal genome testing. *Am. J. Bioeth.* 9(6–7), 23–25 (2009).

31 McGowan ML, Lambrix MM. Are social networkers and genome testers one in the same? The limitations of public opinion research for guiding clinical practice. *Am. J. Bioethics* 9(6–7), 21–23 (2009).

Websites

101 Intercensal Estimates of the Resident Population for Counties: April 1, 2000 to July 1, 2010. United States Census Bureau, Washington DC, USA (2011). www.census.gov/popest/data/intercensal/county/CO-EST00INT-01.html

102 Educational Attainment 2005–2009: American Community Survey 5-year Estimates. United States Census Bureau, Washington DC, USA (2011). www.census.gov/acs/www/data_documentation/2009_release