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ORIGINAL ARTICLE

# Was it worth it? Patients' perspectives on the perceived value of genomic-based individualized medicine

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**Abstract** The value of genomic sequencing is often understood in terms of its ability to affect diagnosis or treatment. In these terms, successes occur only in a minority of cases. This paper presents views from patients who had exome sequencing done clinically to explore how they perceive the utility of genomic medicine. The authors used semi-structured, qualitative interviews in order to study patients' attitudes toward genomic sequencing in oncology and rare-disease settings. Participants from 37 cases were interviewed. In terms of the testing's key values—regardless of having received what clinicians described as meaningful results—participants expressed four qualities that are separate from traditional views of clinical utility: Participants felt they had been empowered over their own health. They felt they had contributed altruistically to the progress of genomic technology in medicine. They felt their suffering had been legitimated. They also felt a sense of closure, having done everything they could. Patients expressed overwhelmingly positive attitudes toward sequencing. Their rationale was not solely based on the results' clinical utility. It is important for clinicians to understand this non-medical reasoning as it pertains to patient decision-making and informed consent.

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## Introduction

Genomic-based individualized medicine is increasingly becoming incorporated into clinical care. Medical professionals who use this new tool often equate the utility of genomic sequencing with the clinical actionability of its results (Sanderson et al. 2005; Green et al. 2013; Berg et al. 2011; Lindor et al. 2013). The usefulness of sequencing in the eyes of these professionals tends to depend on their ability not merely to make meaning of the test results (analytical utility) but also to act on them for the benefit of the patient (clinical utility or medically actionable). Therefore, clinicians evaluate genomic sequencing's utility based on its potential to return information that changes the individual's healthcare (Ravitsky and Wilfond 2006). For clinicians, "Was it worth it?" means, in effect, "Did it inform treatment, or did it provide a diagnosis?" However, patients and their family members often do not attribute value in the same way.

Although experts in evidence-based medicine and genetics hold varying opinions on how to define "clinical utility" (Grosse Scott and Muin Khoury 2006; Bunnik et al. 2014), value is often understood narrowly in the framework of health outcomes relative to costs (Porter 2010). It has been increasingly acknowledged that the value of genomic medicine must be considered in context, specifically through the perspective of the individual patient (Botkin et al. 2010; Grosse et al. 2010; Foster Morris et al. 2009; Veenstra et al. 2013; Conti et al. 2010). The personal utility of information to the patient and his/her family needs to be considered in order to evaluate the worth of genomic medicine more comprehensively.

In the great majority of situations, exome and genome sequencing currently fails to identify a cause for disease. A number of institutions report successful outcomes, all, however, in or around the lowest quartile. For instance, in 2013, the Medical College of Wisconsin reported that its program was able to achieve a definitive diagnosis in 27 % of patients undergoing genomic sequencing (Jacob Howard et al. 2013). Other sources report similar numbers (Miyatake and Matsumoto 2014; Biesecker and Green 2014; De Ligt et al. 2012). A recent paper claims that across a variety of disorders, sequencing was able to identify pathogenic variants in 21 % of cases, noting that success is more likely for Mendelian disorders (34 %) or when family trios are sequenced (54 %) (Taylor et al. 2015). Another study reported similar diagnostic yields (25.2 %) as the previous studies; however, these authors reported that the percentage of findings that were *medically actionable* (results that the physician can use to help treat the disorder) was as low as 4.6 % (Yang et al. 2014). Due to the current relatively low yield of medically actionable results from exome sequencing, insurance companies in the USA do not always provide coverage (Chakradhar 2015). Similar concerns with emerging evidence-based, personalized medicine initiatives are seen throughout the European Union as well (Payne and Annemans 2013). Therefore, genomic sequencing can be cost-prohibitive for patients, and it might not even be offered to them for this reason. Furthermore, many forms of high-throughput sequencing take many weeks and even months to return results. That time is crucial, and for some (particularly oncology patients where the sequencing is used to help identify a targetable mutation or in other rare circumstances), the difference of a month could represent the difference between life and death. In these ways, it is clear that by engaging in genomic sequencing, patients invest a notable amount of resources.

However, as we demonstrate in this paper, patients may place great value on genomic sequencing regardless of the low probability of a diagnostic or actionable outcome. In fact, such probability does not factor into many patients' "illness narratives" (Kleinman 1988) at all. Patients may have a significant emotional, physical, and financial investment in genomic sequencing. Despite this, they find value in undergoing the tests even when the outcome yields nothing that is diagnostic or clinically actionable.

A number of studies have sought to define the attitudes of patients and research participants regarding genomic sequencing results and have found that the majority desire that information even when there is no clinical utility (Middleton et al. 2015; Clift et al. 2015; Graves et al. 2015; Beskow et al. 2009; Kaufman et al. 2012; Ormond et al. 2010; Bollinger et al. 2013; Jarvik et al. 2014; Sanderson et al. 2013). Personal utility is sometimes cited as one of the important justifications for returning results from exome sequencing, even in research contexts. Personal utility has varied definitions (Bennette et al. 2013; Beskow Laura and Wylie 2010; Foster Morris et al. 2009), and we use the term to indicate those perceived values not traditionally considered clinical. When surveyed, the majority of genetic professionals agree that individual choice and personal utility are important considerations in clinical sequencing (Yu et al. 2014). However, it remains doubtful that insurers will reimburse for genomic sequencing based on personal utility alone (Grosse et al. 2009; Rogowski et al. 2009).

In this paper, we examine the ways in which patients perceive the value of the entire experience of clinical exome sequencing. We demonstrate that patient values go beyond a financial calculus of cost–benefit ratios. Patients and their family members give similar—and in fact at times greater—weight to emotional, physical, and societal investment.

## Methods

We designed our study to investigate patient attitudes toward genomic medicine and have described in detail our approach elsewhere (Clift et al. 2015). Our methodology entailed interviews with patients and their families. We conducted in-depth (Britten 1995), semi-structured interviews with individuals and their family members as they underwent genomic sequencing at the Mayo Clinic's Individualized Medicine (IM) Clinic. The IM Clinic specializes in bringing new sequencing technologies into medical practice (Lazaridis et al. 2014). At the time of our study, the IM Clinic provided two services: one for cancer patients for whom previous therapies had failed, and one for "diagnostic odyssey" patients with conditions presumed to be genetic but without diagnosis. Certain types of results were necessarily returned, while genetic counselors worked with patients to determine whether they wanted to "opt in" on receiving certain other types of results (see Table 1).

Interview guides and participant contact materials were developed and subsequently approved by the Mayo Clinic Institutional Review Board. We developed an interview guide

**Table 1** Types of possible results returned from genomic sequencing

| | Type of results | Status |
|---|---|---|
| 1 | Deleterious mutations related to phenotype | Required to return |
| 2 | Variants of unknown significance suspected to be related to phenotype | Required to return |
| 3 | Medically actionable deleterious mutation unrelated to phenotype | Optional |
| 4 | Carrier status for Mendelian disorders | Optional |
| 5 | Pharmacogenetic variants | Optional |

of open-ended questions and follow-up probes. The questions were designed to assess patients' experiences in the IM Clinic, their general understanding of the sequencing they were undergoing, their hopes and concerns, and their attitudes toward the return of results. The interview guide was modified iteratively as data were collected and analyzed and as new themes emerged as salient.

We began conducting interviews in December 2012, with the majority being completed by March 2014. An additional 13 follow-up interviews were conducted between July 2015 and August 2015. We invited individuals to participate in our study after they had their initial appointment with an IM Clinic physician. Interested individuals were consented and signed a HIPAA form. Interviews were done either in person or by telephone, depending on the individual's preference and time constraints. Interviews averaged 20 min, though the participant could keep the conversation as short or as long as he or she wished. We spoke to patients at a number of points during the process of genomic sequencing: before their initial meeting with the genetic counselor, after that meeting, while the patient waited for results, and after the return of those results. Patients received a report of their results (see Table 1) and met with a clinician to explain the report. The purpose of conducting multiple interviews was to see how their opinions and beliefs regarding sequencing might change over time. We anticipated that it would not be possible to reach each patient at each of the four interview points.

Interviews often included more than one participant at the request of the patient. Such group interviews were counted as a single interview. For oncology patients, the additional participant was generally a spouse or significant other. The diagnostic odyssey participants were more often parents of the proband. Seven diagnostic odyssey patients, who were old enough and cognitively able to participate, were interviewed individually, though family members occasionally joined at the request of the proband. Having multiple participants present added to the conversational atmosphere of our interviews, with questions being addressed to all participants and with each able to respond according to their unique positions within the context of genomic sequencing.

Interviews were audio-recorded and subsequently transcribed, de-identified, and analyzed using standard qualitative methods. After reading the transcripts, researchers created a codebook using aspects of grounded theory and inductive qualitative analysis, helping us to avoid preconceptions and to find unanticipated themes and commonalities (Corbin and Strauss 2007). The coded text was then compiled and analyzed in QSR NVivo 10, a qualitative data analysis software program. Researchers were informed by traditional anthropological analytic methods that focus on reflexivity (Davies 2007). The major theme of this paper emerged upon reconsideration of the coded materials.

## Results

Our data come from 39 cases, each represented by at least 1 interview. Some participants were interviewed as many as three times, based on their availability and interest. Sixteen cases were interviewed at least twice. Everyone we approached agreed to participate in the project; however, time constraints prevented researchers from approaching every patient who came through the IM Clinic. We conducted a total of 68 interviews. Thirty-nine participants completed at least one, 20 completed at least two, and 9 completed three interviews. Oncology patients ranged in age from 29 to 67, and diagnostic odyssey patients ranged in age from 20 months to 45 years. As mentioned above, we interviewed family members of those patients unable to consent and participate due to age or cognitive capacity. Six patients—three from each service—did not proceed with genomic sequencing after the intake counseling session. This was due to insurance issues and other eligibility criteria, including their candidacy for surgery or biopsy. For more details, refer to Table 2. Individuals are identified by their service (diagnostic odyssey: Dx; oncology: O), by their approximate age (#), and by their sex (female: F; male: M).

Despite coming from different cohorts, responses from both cancer and diagnostic odyssey patients were quite similar. Based on our sample data, no difference was found in attitudes based on a patient's receiving a definitive diagnosis or treatment options. Patients not only recognized the clinical utility described to them by their clinicians; they also found value in several other, surprising aspects of their experiences. Four major themes quickly became apparent as to why a participant felt the sequencing had been useful, none of which could be considered analogous to goals of the results' immediate effects on treatment or diagnosis.

The first is personal utility and the belief that knowing one's personal genetic composition (including non-actionable variants of unknown significance) could allow a patient to make more informed decisions about his or her future healthcare. The second is the feeling of "doing one's part," the satisfaction of being able to contribute knowledge to a new field and help research efforts. The third is the social legitimation granted by candidate genetic causes of a disorder (with or without a definitive diagnosis). Relatedly, patients consistently expressed a sense of closure provided by

**Table 2** Participant characteristics

| | Oncology | Diagnostic odyssey |
|---|---|---|
| Age range of proband | 29–67 years | 20 months–45 years |
| Gender of proband (male/female) | 7/11 | 8/12 |
| Total cases | 19 | 20 |
| Total interviews | 32 | 36 |

completing sequencing. Even if they received no new information back, they felt a relief believing they had done everything currently available to search for answers.

### Personal utility

For many of the patients and their families, a significant amount of their diagnostic or treatment journey was traversed without having tangible information to guide them. Having information about their own genetics was one more piece of data about themselves that could inform future treatment. The information from genomic sequencing or panels empowered patients even if the results did not yield any specific answers. Participants expressed that with this information, they could be their own advocates and look for their own answers.

"I want to know everything about myself, because I mean, if you can plan and be aware of things, you can also inform yourself about new developments that are happening, or new things you can do to—to offset those genetic profiles" (O60M), said one oncology patient. Many patients appreciated the possibility that they can hold onto their inconclusive results and return with questions at their regular visits with their physicians. "You may not have all the answers now for us, but maybe in the future you will," said one woman (Dx40F). The parent of another patient told us, "So we may not discover anything now; maybe his sequencing could be used at a later date" (parent of Dx11M). Another participant stated that she would like to receive all of her results "so that I could start paying more attention to research that's coming out" (O36F), suggesting that she would be better positioned to interpret new knowledge being published in medical literature.

In addition to doing their own background research, some patients began self-advocating with the information gained from genomic sequencing. Even though the results might have been inconclusive, belief in the necessity of further research was a key motivator. One patient explained that her results encouraged her to advocate for research on her disease: "Getting my results from you guys really empowered me to do something. I've taken on—made this big petition to get our research reinstated. And it's really taken off. It's been really empowering" (Dx45F).

The results from genomic sequencing caused some patients to find support groups with others who had conditions similar to theirs. This was the case not only for patients receiving a definitive diagnosis; it also facilitated networking practices of patients who merely received variants of unknown significance. Some patients had success connecting with other individuals with the same or similar conditions as one patient explained, "That made a huge difference. I mean it was absolutely wonderful to be able to talk to another family that has been through the same scenario. […] They actually introduced us to a couple of more families" (mother of Dx5M).

Patients also repeated that, while genomic science is relatively nascent, the answers to their problems might be found in the data it returns: One participant stated that that technology may provide all the needed data, but that no one knows how to interpret them yet. As he summarized, "There are limitations in regards to genetic sequencing […] though the sequence may all be there" (father of Dx11M). Another participant noted the limitations but still maintained hope: "Well I understand that the chances that they are going to come up with something are very low. So in that sense I am not expecting very much but who knows. If you don't try, you won't get anything" (O41F). Knowing their genotype, these patients put forward, allows them to self-advocate. They can find trials, treatments, and research on their own.

### Doing their part

Altruism and the ability to contribute to research is another reason that many of the patients proceeded with sequencing. They did this despite acknowledging that it was relatively unlikely that they would find an answer for *themselves* as this participant illustrates: "My expectations are low. I'm kind of looking at it as potential for research going forward. […] From what my doctor explained to me, the odds don't look too great that they're going to be able to find a different chemo that's going to be able to inhibit my kind of cancer" (O50F).

The ability to further knowledge in the field of genomic medicine was often cited as a reason to participate: "I think in the future this will be extremely important in the treatment of any type of disease, but for right now you have to start somewhere […] But actually for right now my expectations are that I am just sort of helping research" (O61F).

Participating in research was seen as an opportunity to give back. A daughter of an oncology patient posited: "Who knows what they are going to discover soon, and so, if you know about it now, you know, you can always be watching– participate in studies or something […] That can always be a good option if they needed participants […] to help somebody in the future even if it is not yourself" (daughter of O67M).

Many patients similarly saw a potential value in clinical genomic sequencing as helping an unknown, unrelated person in the future. "In the long run if it doesn't help me, that if all the studies and the sequences are somehow able to help somebody else, I feel that I am doing my part here on earth as part of this, that if it can't help me, then hopefully the testing can help somebody else" (O43F). The father of a diagnostic odyssey patient put it this way: "It is an opportunity for us to learn more about [the patient] that might benefit her and also benefit other people" (father of Dx5yF). An oncology patient echoed this sentiment: "[I] hope that it could help someone else in the future if it doesn't help me, that the research could even help someone else down the line going through something similar" (O29F). In fact, one woman even *expected* research to be

conducted on her clinical sample: "You know, I decided to go forward even though I was told there's a low probability that they'd be able to change anything in my care […] And once Mayo gathers the material, it's not like you take it and throw it away. It will be used in the future to make care better for other people" (Dx45F). This belief was in fact quite common among our interviewees. These examples illustrate how patients see the value in research and want their contributions to be utilized.

### Legitimation and closure

Even if a deleterious mutation is identified as the probable genetic cause of the disease, treatment options still may not change or may not be available. Nonetheless, "having a name" or a cause lends a sense of legitimacy to patients' suffering. "A name" or cause can translate into a social worker, a government-appointed personal care assistant, and insurance benefits, among other things.

One patient had the expectation on the outset that exome sequencing would "help identify and give me validation" (Dx40F). When her results came back inconclusive with the exception of a variant of unknown significance, she told us, "To me, [sequencing] was validating, because, you guys may not have the science, but I know what I feel […] and it is very compatible with what you guys showed that's not significant." She felt that, despite the genetic counselor's statements to the contrary, that she could derive valuable information from the uncertain results that explained her symptoms. This patient was not alone; several participants felt legitimated by their results despite the fact that doctors had characterized them as inconclusive.

A common theme in our patient data is that participating in genomic sequencing allows the patient to feel closure, to feel as though he or she has done what was necessary to ensure his or her health. One patient's mother told us that proceeding with genomic sequencing "gives me the comfort of knowing, okay, I've truly done everything I can do. This is kind of the last frontier, and who doesn't do everything they can when it comes to the health of their child?" (mother of Dx18F).

The mother of one patient said the value of receiving a diagnostic result, even if it was not actionable, was that "for him, not to be poked and prodded to try to figure out what is wrong with him anymore is good" (mother of Dx5M). An oncology patient thought it might "help eliminate me having to go through so many procedures" (O29F).

Although these accolades are often tempered with the admission that genomic science is too nascent to answer all health questions at the moment, it was believed that sequencing now could provide the potential for answers in the future. Even if "bittersweet," as one participant put it (mother of Dx5M), the return of even inconclusive genomic sequencing results provides patients with a sense that they have done everything possible to ensure their health.

## Discussion

Participants overwhelmingly reported feeling that undergoing genomic sequencing had been worthwhile. So-called negative results did not determine patient attitudes. This fact contrasts importantly with a common equation by medical professionals of success with clinical actionability, giving cost some consideration as well (Sanderson et al. 2005; Green et al. 2013; Berg et al. 2011; Lindor et al. 2013). Rather than merely on a calculus of clinically actionable outcomes and costs (Bunnik et al. 2014; Grosse Scott and Muin Khoury 2006; Porter 2010), patients based the value of genomic sequencing on psychosocial outcomes as well. The vast majority of interviewees expressed satisfaction with—and even indebtedness to—the sequencing, regardless of the clinical actionability of the results it provided. The sequencing (with its costs, waittime, and uncertainty) was indeed "worth it," they testified.

Other than recognizable medical value, patients found value in four general (perceived) applications of their results. These values were consistently expressed and do not fall under the category of clinical actionability, suggesting that more is ethically at stake in overseeing the return of results than has traditionally been considered. Patients found meaning in results regardless of their clinical utility. First, many patients believed that—even when clinicians could not use the test results to alter medical care—they could take greater responsibility for their health or simply find value in the information itself apart from professional interpretation. Second, participants expressed repeatedly that one value of genomic sequencing was its contribution to knowledge in the field. Third, even when a diagnosis provided no treatment options, patients found a sense of legitimation in the medicalized procedure.

Some patients whose healthcare regimen was unaffected still valued having a definitive name for their symptoms. Legal recognition of the disorder through conclusive diagnosis but without treatment also opened avenues to state welfare. Other studies have found that patients recognize non-clinical, psychosocial, and behavioral values of single-gene and smaller panel genetic testing as well (Kopits et al. 2011; Roberts and Uhlmann 2013). Similarly, many patients experienced closure, feeling relief, and believing that they had done everything they could.

It is important to note that our participants regularly gave significant weight to their own interpretations of sequencing results while simultaneously recognizing that their interpretations differed from that of their healthcare providers. Although clinicians characterized findings as insignificant and non-actionable, our interviewees retorted that there indeed was

important—albeit non-clinical—information to be gleaned from them. This secondary, nonspecialist interpretation provided them with a sense of legitimation that their clinicians might not have expected.

Another interesting result from our study is that many of our participants still saw genomic sequencing as the most advanced and end-of-the-line testing available. Despite newly emerging literature and research studies on epigenetics, proteomics, and microbiomics, they felt that genomic sequencing represented "all they could do." This underscores the impact of differing understandings between clinician and patient on patients' experience of their healthcare.

From the results of our study, patients stressed the importance of personal utility as one of the motivating factors for proceeding with genomic sequencing. This contrasts with the perceptions of their clinicians and highlights the need for a better definition of personal utility. It also highlights the need to understand how to capture these clinically intangible benefits. How personal utility, or some aspects of it, might be included in the calculus insurers use when deciding to pay for the testing is a question that deserves more deliberative consideration and study. Though challenging, the non-clinical utility to individual patients could be captured by systematic qualitative mechanisms. Using these in a calculus to determine overall value of the clinical genomic sequencing would need to be evaluated in the larger context of health systems and cost effectiveness. Indeed, it may be that a consideration of personal utility should be limited to certain types of clinical situations (e.g., oncology, diagnostic odyssey) and not others (e.g., preventative or predictive medicine).

Participants believed that having genomic sequencing done was inherently valuable to furthering genomic knowledge and that it served as a contribution to research that could be beneficial to others in the future. Altruism clearly is not the only motivating factor for participation (Hunter et al. 2012; Mein et al. 2012; Wasson et al. 2012). Nonetheless, for our interviewees, it was a significant reason for participating despite there being no guaranteed clinical or personal utility to sequencing.

Whether or not these feelings are considered reasonable responses to the results, it is important for clinicians to recognize that patients may react to the results of sequencing in these ways. Consent and disclosures should be delivered with these potential reactions in mind. In order to understand patients' decision-making processes, we must attend to motivations and applications such as these. It is not our argument that these are necessarily accurate interpretations of sequencing results; accuracy is not key here. We simply found these interpretations common enough that clinicians need to be aware that patients can be and are influenced by them. Does having these preconceptions affect one's ability to make informed and well-reasoned decisions about finances, surgery, and other healthcare concerns? This is perhaps an overlooked aspect of patients' decision-making. Further longitudinal studies should be conducted in order to determine the lasting salience of sequencing results for patients' healthcare practices. In obtaining consent for and disclosing results from sequencing, it is incumbent on clinicians to ensure that patients are informed in their decision-making. It is therefore necessary to recognize that patients may interpret the value of genomic sequencing in ways not intended by their clinicians.

While noteworthy in their own right, it should be noted that our results are limited by several factors. We were unable to conduct interviews with each patient who went through the Mayo IM Clinic. Similarly, participants were drawn solely from the IM Clinic and thus represent an atypical population when compared to the general consumers of genomic-based medicine. Many participants in our sample had previous experience with genetic testing, and this may have affected some of their responses. It might have proved of interest to compare responses over time, and this information was not collected. In addition, we were unable to determine the exact number of patients in our study who received results determined to be clinical actionable by their care team. More studies are needed to examine the breadth of reactions from patients undergoing different types of testing.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no competing interest.

**Human and animal rights 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 (5). All participants provided informed consent for being included in the study.

## References

Bennette CS, Trinidad SB, Fullerton S, Patrick D, Amendola L, Burke W, Hisama F, Jarvik G, Regier D, Veenstra D (2013) Return of incidental findings in genomic medicine: measuring what patients value—development of an instrument to measure preferences for information from next-generation testing (IMPRINT). Genet Med 15:873–881

Berg JS, Khoury MJ, Evans JP (2011) Deploying whole genome sequencing in clinical practice and public health: meeting the

challenge one bin at a time. Genet Med 13(6):499–504. doi:10.1097/GIM.0b013e318220aaba

Beskow Laura M, Wylie B (2010) "Offering individual genetic research results: context matters.". Sci Transl Med 2(38):38c20

Beskow LM, Grady C, Iltis AS, Sadler JZ, Wilfond BS (2009) Points to consider: the research ethics consultation service and the IRB. IRB 31(6):1–9

Biesecker LG, Green RC (2014) Diagnostic clinical genome and exome sequencing. N Engl J Med 370(25):2418–25. doi:10.1056/NEJMra1312543

Bollinger JM, Green RC, Kaufman D (2013) Attitudes about regulation among direct-to-consumer genetic testing customers. Genet Test Mol Biomarkers 17(5):424–28. doi:10.1089/gtmb.2012.0453

Botkin Jeffrey R, Steven Teutsch M, Celia Kaye I, Maxine H, James Haddow E, Linda Bradley A, Kathleen Szegda W, David D, EGAPP Working Group (2010) Outcomes of interest in evidence-based evaluations of genetic tests. Genet Med Off J Am Coll Med Genet 12(4):228–35. doi:10.1097/GIM.0b013e3181cdde04

Britten N (1995) Qualitative research: qualitative interviews in medical research. BMJ 311(6999):251–53. doi:10.1136/bmj.311.6999.251

Bunnik, Eline M., A. Cecile J. W. Janssens, and Maartje H. N. Schermer. 2014. "Personal utility in genomic testing: is there such a thing?" *Journal of Medical Ethics*, May, medethics – 2013–101887. doi: 10.1136/medethics-2013-101887

Chakradhar S (2015) Insurance companies are slow to cover next-generation sequencing. Nat Med 21(3):204–5. doi:10.1038/nm0315-204

Clift, Kristin E., Colin M. E. Halverson, Alexander S. Fiksdal, Ashok Kumbamu, Richard R. Sharp, and Jennifer B. McCormick. 2015. "Patients' views on incidental findings from clinical exome sequencing." *Applied & Translational Genomics* 4 (March): 38–43. doi:10.1016/j.atg.2015.02.005

Conti R, Veenstra DL, Armstrong K, Lesko LJ, Grosse SD (2010) Personalized medicine and genomics: challenges and opportunities in assessing effectiveness, cost-effectiveness, and future research priorities. Med Decis Mak Int J Soc Med Decis Mak 30(3):328–40. doi:10.1177/0272989X09347014

Corbin J, Strauss A (2007) Basics of Qualitative Research: Techniques and Procedures for Developing Grounded Theory, 3rd edn. SAGE Publications, Inc., Los Angeles, California

Davies CA (2007) *Reflexive Ethnography: A Guide to Researching Selves and Others*. New York: Routledge.

De Ligt, Joep, Marjolein H. Willemsen, Bregje W.M. van Bon, Tjitske Kleefstra, Helger G. Yntema, Thessa Kroes, Anneke T. Vulto-van Silfhout, et al. 2012. "Diagnostic exome sequencing in persons with severe intellectual disability." *New England Journal of Medicine* 367 (20): 1921–29. doi:10.1056/NEJMoa1206524

Foster Morris W, John Mulvihill J, Richard Sharp R (2009) Evaluating the utility of personal genomic information. Genet Med Off J Am Coll Med Genet 11(8):570–74. doi:10.1097/GIM.0b013e3181a2743e

Graves KD, Sinicrope PS, McCormick JB, Zhou Y, Vadaparampil ST, Lindor NM (2015) Public perceptions of disease severity but not actionability correlate with interest in receiving genomic results: nonalignment with current trends in practice. Public Health Genomics 18(3):173–83. doi:10.1159/000375479

Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, Amy McGuire L (2013) ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med Off J Am Coll Med Genet 15(7):565–74. doi:10.1038/gim.2013.73

Grosse SD, Kalman L, Khoury MJ (2010) Evaluation of the validity and utility of genetic testing for rare diseases. Adv Exp Med Biol 686:115–31. doi:10.1007/978-90-481-9485-8_8

Grosse, Scott D., and Muin J. Khoury. 2006. "What is the clinical utility of genetic testing?" *Genetics in Medicine: Official Journal of the American College of Medical Genetics* 8 (7): 448–50. doi: 10.109701.gim.0000227935.26763.c6

Grosse SD, McBride CM, Evans JP, Khoury MJ (2009) Personal utility and genomic information: look before you leap. Genet Med Off J Am Coll Med Genet 11(8):575–76. doi:10.1097/GIM.0b013e3181af0a80

Hunter J, Corcoran K, Leeder S, Phelps K (2012) Appealing to altruism is not enough: motivators for participating in health services research. J Empir Res Hum Res Ethics: JERHRE 7(3):84–90. doi:10.1525/jer.2012.7.3.84

Jacob Howard J, Kelly A, David Bick P, Kent B, David Dimmock P, Michael F, Jennifer G et al (2013) Genomics in clinical practice: lessons from the front lines. Sci Transl Med 5(194):194cm5. doi:10.1126/scitranslmed.3006468

Jarvik GP, Amendola LM, Berg JS, Brothers K, Clayton EW, Chung W, Barbara Evans J et al (2014) Return of genomic results to research participants: the floor, the ceiling, and the choices in between. Am J Hum Genet 94(6):818–26. doi:10.1016/j.ajhg.2014.04.009

Kaufman DJ, Bollinger JM, Dvoskin RL, Scott JA (2012) Risky business: risk perception and the use of medical services among customers of DTC personal genetic testing. J Genet Couns 21(3):413–22. doi:10.1007/s10897-012-9483-0

Kleinman A (1988) The illness narratives: suffering, healing & the human condition. Basic Books, New York

Kopits IM, Chen C, Roberts JS, Uhlmann W, Green RC (2011) Willingness to pay for genetic testing for Alzheimer's disease: a measure of personal utility. Genet Test Mol Biomarker 15(12):871–875

Lazaridis KN, McAllister TM, Babovic-Vuksanovic D, Beck SA, Borad MJ, Bryce AH, Asher Chanan-Khan A et al (2014) Implementing individualized medicine into the medical practice. Am J Med Genet Part C, Seminar Med Genet 166(1):15–23. doi:10.1002/ajmg.c.31387

Lindor NM, Johnson KJ, McCormick JB, Klee EW, Ferber MJ, Farrugia G (2013) Preserving personal autonomy in a genomic testing era. Genet Med Off J Am Coll Med Genet 15(5):408–9. doi:10.1038/gim.2013.24

Mein G, Seale C, Rice H, Johal S, Ashcroft RE, Ellison G, Tinker A (2012) Altruism and participation in longitudinal health research? Insights from the Whitehall II Study. Soc Sci Med (1982) 75(12):2345–52. doi:10.1016/j.socscimed.2012.09.006

Middleton, Anna, Caroline F. Wright, Katherine I. Morley, Eugene Bragin, Helen V. Firth, Matthew E. Hurles, and Michael Parker. 2015. "Potential research participants support the return of raw sequence data." *Journal of Medical Genetics*, May, jmedgenet – 2015–103119. doi:10.1136/jmedgenet-2015-103119

Miyatake S, Matsumoto N (2014) Genetics: clinical exome sequencing in neurology practice. Nat Rev Neurol 10(12):676–78. doi:10.1038/nrneurol.2014.213

Ormond KE, Wheeler MT, Hudgins L, Klein TE, Butte AJ, Altman RB, Ashley EA, Greely HT (2010) Challenges in the clinical application of whole-genome sequencing. Lancet 375(9727):1749–51. doi:10.1016/S0140-6736(10)60599-5

Payne K, Annemans L (2013) Reflections on market access for personalized medicine: recommendations for Europe. Value Health 16:S32–S38

Porter ME (2010) What is value in health care? N Engl J Med 363(26):2477–81. doi:10.1056/NEJMp1011024

Ravitsky V, Wilfond BS (2006) Disclosing individual genetic results to research participants. Am J Bioethics: AJOB 6(6):8–17. doi:10.1080/15265160600934772

Roberts JS, Uhlmann WR (2013) Genetic susceptibility testing for neurodegenerative diseases: ethical and practice issues. Prog Neurobiol 110:89–101

Rogowski WH, Grosse SD, Khoury MJ (2009) Challenges of translating genetic tests into clinical and public health practice. Nat Rev Genet 10(7):489–95. doi:10.1038/nrg2606

Sanderson SC, Diefenbach MA, Zinberg R, Horowitz CR, Smirnoff M, Zweig M, Streicher S, Jabs EW, Richardson LD (2013) Willingness to participate in genomics research and desire for personal results among underrepresented minority patients: a structured interview study. Journal of Community Genetics 4(4):469–82. doi:10.1007/s12687-013-0154-0

Sanderson S, Zimmern R, Kroese M, Higgins J, Patch C, Emery J (2005) How can the evaluation of genetic tests be enhanced? Lessons learned from the ACCE framework and evaluating genetic tests in the United Kingdom. Genet Med 7(7):495–500. doi:10.1097/01.gim.0000179941.44494.73

Taylor, Jenny C., Hilary C. Martin, Stefano Lise, John Broxholme, Jean-Baptiste Cazier, Andy Rimmer, Alexander Kanapin, et al. 2015. "Factors influencing success of clinical genome sequencing across a broad spectrum of disorders." *Nature Genetics* advance online publication (May). doi:10.1038/ng.3304

Veenstra DL, Piper M, Haddow JE, Pauker SG, Klein R, Richards CS, Sean Tunis R et al (2013) Improving the efficiency and relevance of evidence-based recommendations in the era of whole-genome sequencing: an EGAPP methods update. Genet Med Off J Am Coll Med Genet 15(1):14–24. doi:10.1038/gim.2012.106

Wasson K, Hogan NS, Sanders TN, Helzlsouer KJ (2012) Primary care patients' views, attitudes, and decision-making factors regarding direct-to-consumer personal genome testing: results from a qualitative study. AJOB Prim Res 3(2):24–35. doi:10.1080/21507716.2011.650344

Yang Y, Muzny DM, Xia F et al (2014) Molecular findings among patients referred for clinical whole-exome sequencing. JAMA 312(18):1870–79. doi:10.1001/jama.2014.14601

Yu J-H, Harrell TM, Jamal SM, Tabor HK, Bamshad MJ (2014) Attitudes of genetics professionals toward the return of incidental results from exome and whole-genome sequencing. Am J Hum Genet 95(1):77–84. doi:10.1016/j.ajhg.2014.06.004