Review

The clinical utility of whole-exome sequencing in the context of rare diseases – the changing tides of medical practice

Nguyen M.T., Charlebois K. The clinical utility of whole-exome sequencing in the context of rare diseases – the changing tides of medical practice. Clin Genet 2015: 88: 313–319. © 2014 The Authors. Clinical Genetics published by John Wiley & Sons A/S. Published by John Wiley & Sons Ltd., 2014

Whole-exome sequencing (WES) carries the potential to facilitate the identification of disease causing genes. This is particularly relevant concerning rare diseases, which proves particularly difficult for physicians to diagnose. However, the complexity of this technology renders its applicability onto the clinical setting uncertain. Our study thus aims to understand physicians’ perspectives regarding the clinical utility of WES, particularly for providing a diagnosis for patients with rare diseases. Ten semi-structured interviews were conducted with physicians with experience and familiarity with WES, and the major themes that emerged from our interviews were (i) the relevance of WES in diagnosing patients with rare diseases (appropriateness); (ii) the cost-effectiveness of WES (accessibility), (iii) the practical issues related to the clinical implementation of WES (practicability); and (iv) ethical, legal and social issues (acceptability). Our study highlights how the clinical implementation of WES presents additional challenges where rare diseases are taken into consideration.

Conflict of interest

The authors declare no conflicts of interest.

Clinical laboratories are increasingly offering whole-exome sequencing (‘WES’) to identify disease-causing genes as an alternative to traditional individual gene or gene panel testing (1–3). Currently used mainly within the research setting in Canada, it is thus likely that this technology will soon be widely used in the clinical setting (4). But before a new genetic technology is generally accepted into clinical practice, one conventional criterion for its integration is its usefulness or ‘clinical utility’. In its strictest sense, clinical utility is often referred to as the ability of a diagnostic test to ‘prevent or ameliorate adverse health outcomes’ (5). In other words, will the test results affect a medical outcome or make a change in the treatment plan for the patient? Nonetheless, there is a growing body of literature that supports a broader definition of clinical utility, particularly with respect to next generation sequencing techniques like WES (6).

WES generates a wealth of information with varying degrees of significance, and any judgment of its clinical utility should be context specific and perspective dependent (7). It will be the physicians who must ask: Why use WES? How will it affect clinical practice for a particular group of patients? and in pondering this, physicians must weigh the overall benefits and drawbacks that exist. Besides accounting for changes in medical management, additional outcomes such as psychosocial or familial outcomes could be of equal importance when considering the utility of WES. This expanded conceptualization of clinical utility should then account for the opinions and judgments of the physicians or practitioners who will be using the tool for their patients. In fact, it will be the
physicians’ views, opinions, needs and motivations that will play an important role in driving the adoption of WES into routine medical practice.

In this study, we make enquiries about factors that influence physicians’ assessments or judgments about WES. We explore the viewpoints of Canadian physicians regarding how WES should be implemented and what operational or practical issues must be addressed before WES is widely used. The clinical utility of WES will be analyzed on the basis of the following four dimensions: (i) appropriateness, (ii) accessibility, (iii) practicality, and (iv) acceptability (these four dimensions, adopted from Smart’s multidimensional model, are summarized in Table 1 below with the concordant issues that will be examined). Although we draw from Smart’s model to analyze the clinical utility of WES, we adapted and modified it in order to take into consideration issues surrounding genetic technologies. Our focus is on the use of WES for the diagnosis of rare diseases as this population of patients are the ones who derive most benefit from this diagnostic sequencing tool.

Material and methods
Recruitment, sampling and data collection

A list of potential interviewees was generated through personal contacts with research collaborators, internet searches and consultation with professional listings from different Canadian medical associations, e.g. the Canadian College of Medical Geneticists. This served as a convenience sampling frame upon which to select participants. A purposive criterion sampling strategy was then used to select participants based on the following inclusion criteria: physicians (MDs); direct experience with rare disease patients (adult, pediatric, or both); experience with genetic testing for diagnostic purposes for patients with rare diseases; and familiarity with next-generation sequencing technologies, such as WES. Many of the 32 participants that met our criteria did not respond to our initial invitation, some of them declined to take part in an interview since they felt they lacked familiarity with WES. Ten semi-structured interviews were conducted, between November 2013 and March 2014, with physicians across Canada via telephone.

The interview questions included the following topics: experiences caring for patients with rare diseases, knowledge and experiences using genetic testing (particularly WES) as a diagnostic tool and opinions regarding the risks and benefits of WES as a diagnostic tool for patients with rare diseases. The questions were formulated to consider the research aims and questions as well as current literature on the topic of rare diseases and genetic testing. Smart’s model (7) was also used as a basis to develop the interview guide.

Data analysis

Thematic analysis was used to analyze the data from the interviews (8, 9). Verbatim transcripts of the interviews were read several times and transcript summaries of the verbatim transcripts were written (9). The data were then coded on the basis of an initial codebook, which was developed according to the research aims and questions as well as elements found in the literature. At the same time, new codes were also generated from the data. N’Vivo software was used to code the data. Codes were then clustered and consolidated under headings that would constitute potential themes (9). Initial themes were thus generated inductively in order to remain close to the data. They were then contrasted and further refined using the dimensions found in Smart’s (7) multi-dimensional model of clinical utility. The themes generated resulted from an iterative process between the emergent themes and the different dimensions. It was then a matter of establishing the relationships between the major themes in order to understand how physicians’ views of the clinical utility of WES were shaped. When the coding process generated nothing new to theme development, it was deemed that thematic saturation had been achieved (10, 11). In that sense, 10 semi-structured interviews proved sufficient.

Results

The major themes that emerged from our interviews with physicians were (i) the relevance of WES in diagnosing patients with rare diseases (appropriateness); (ii) the cost-effectiveness of WES (accessibility), (iii) the practical issues related to the clinical implementation of WES (practicability); and (iv) ethical, legal and social issues (acceptability).

Theme 1: the relevance of WES in diagnosing patients with rare diseases (appropriateness)

According to interviewees, there are many impediments to providing a clear diagnosis to patients with rare diseases. One such impediment is the vagueness of rare disease clinical features which renders its discovery difficult in the first place:

I guess one of the challenges is recognition, and that’s at several levels: the primary care provider recognizing that this is a rare disease, the specialist trying to figure out which rare disease it is. Part of the problem is a lot of the rare diseases have subtle features; some of them rely on very subtle dysmorphology features which may be difficult and subjective, so making a diagnosis can be quite difficult.

Thus, this holds consequences on whether a patient with a rare disease will be referred to a geneticist and have access to a genetic test. Even then, the ambiguity of rare conditions presents a challenge for physicians who need to decide on which genetic test to order:

… molecular testing had always, prior to this time, been done more or less by sequencing a specific gene or set of genes based on suspicion of the physician. What you’re depending on, prior to exome sequencing, is that the disease would be recognizable by the physician – so that they could order a specific test. Once you are outside the pale of known medical knowledge or outside the knowledge of that physician, the likelihood of them being able to order the correct test is nil.
Lack of familiarity with rare diseases among healthcare professionals was thus viewed as an impediment to obtaining a clear diagnosis for patients with rare diseases as it reduced their likelihood of getting a referral to a geneticist. To overcome this, certain physicians mentioned the need for greater awareness and education regarding rare disease and genetic testing.

Physicians also mentioned how most patients with rare diseases are barred from obtaining required health and social services because the provision of these services are often dependent on an acknowledgement of a diagnosis. This, in turn, puts pressure on physicians to either take the necessary steps to provide a diagnosis quickly or simply provide any sort of diagnosis to ensure that the patient’s health and social needs are met:

I think every practitioner functions a little bit differently. I think also there’s a parallel situation going on that often – I’ll call it a game, in a way – that outside the healthcare system there’s the educational system and sometimes the social system, that sometimes patients require a diagnosis for getting certain funding in school or to have access to certain therapies or whether it’s respite or social services in the community.

While this same physician was of the view that WES had the potential to alleviate the problems by helping to provide a correct diagnosis more quickly, other physicians underlined the need for the health and social services system to be structured around need rather than diagnosis.

WES was also viewed as a way to bypass the limits of physicians’ judgment in attempting to provide a diagnosis:

There’s an enormous need for WES. The literature is starting to come out now with quite a robust diagnostic rate, and basically we have patients with either non-specific presentations or incredibly complicated presentations. What we find is they actually have two different genetic disorders. I think it’s not that we’re bad clinicians to not be able to make the diagnosis, it’s just there’s a limit to what we can come up with.

At the same time, however, WES was viewed as relevant for diagnosing patients with rare diseases to the extent that WES was used to the benefit of the patient:

I mean, you could spend a lot of money, but I think the phenotyping is very important and the agreed-upon criteria, and then going the next step – Marfan syndrome would be another example of that, that it probably is not going to change the management of the patient – and so it was reassuring to the patient that you don’t have any other findings that add to the diagnosis, and it would be reassuring. But continuing to investigate the patient, applying for approval for testing, undertaking testing, getting a partial answer, would simply increase the patient’s anxiety and not end up in any positive benefit, I think.

Therefore, WES was deemed relevant for patients with rare diseases so long as it was used cautiously in providing a diagnosis for these patients. Underlying this more cautious approach was a concern with the benefit to the patient and, more specifically, a change in the management or treatment. In the case of patients with rare diseases, given the relative absence of treatments and therapies for most rare diseases, this involves access to the health and social services that these patients may need. The relevance of WES thus hinges on the possibility that it gives patients with rare diseases access to adequate services by providing them with a diagnosis in a timely manner.

Theme 2: cost-effectiveness of WES (accessibility)

Physicians’ views regarding the cost and the funding of WES were shaped by their experiences accessing standard disease-targeted genetic testing for their patients. Finding a diagnosis for a patient with a rare disease entails a complicated and lengthy process on account of the difficulty identifying a rare disease by relying on clinical features alone. Because of this difficulty, physicians described the need to order numerous genetic tests in order to find a diagnosis. Subsequently, the costs for these tests also increases with the number of tests being ordered. Added to that is the need for physicians to undertake an application process to obtain funding for genetic tests that are often not available in certain provinces in Canada or not covered by provincial governments. The application process was described by physicians as time consuming and labor intensive, to the point

The clinical utility of whole-exome sequencing
where physicians mentioned having to take this application process into consideration when attempting to provide their patient with a diagnosis:

Although we’re advocates for our patients, we’re also stewards of the healthcare system and the public purse and I think we have to recognize… first of all, any request for testing, it’s labor-intensive to put in the request, requires filling out several pages of documentation, it’s labor-intensive for someone to review the test. There’s a sense sometimes of certain things are not likely to be funded. I think there’s even a lot of self-monitoring at the first level, and even though I admit to doing it, I feel it’s sometimes to the detriment to our patient, meaning that I think it’s unlikely that the approval will be forthcoming and so the request is not even submitted. Many times there’s just a… self-fulfilling prophecy, or whatnot, so you don’t even put through the effort because you’ve seen it in the past for further previous examples having not gone through.

In that way, issues related to the cost of, as well as access to, genetic tests thus have consequences on the clinical decision-making process that physicians must undertake when seeking a diagnosis for their patient.

The approval process for genetic tests in Canada often requires that physicians demonstrate a change in the management of care for the patient. Indeed, in order for a test to be approved for funding, physicians must demonstrate that a change in the patient’s treatment plan will follow once the patient has undergone the test. On that matter, divergent interpretations regarding what constitutes a change in patient management, particularly among those responsible for reviewing the applications, influences whether a test will be approved for funding:

Even then, I think different people’s interpretation of change in management is different and so that can lead to tests not being funded because whoever is reviewing it may view change of management as something very definitive, i.e., the patient, if he has a genetic test, will get an organ transplantation or will get a defibrillator in place, and more nuanced changes to management in terms of tailoring educational programs, having the parents have a better understanding of what’s wrong with their child, which might lead to less unnecessary medical appointments – all these more nuanced ways that management may change are not as clear to the decision-makers, and so that may lead to a test not being approved.

Given the relative absence of available treatments for patients with rare diseases, a more stringent definition of patient management, which is narrowly centered on a defined treatment plan, may impede patients’ access to genetic testing.

Clinicians expressed the view that certain parameters should be set in terms of public funding for WES. In spite of their frustrations in having to demonstrate a change in patient management for genetic test funding, ironically, when asked what criterion should be required if WES is publically funded, most physicians responded that there is a need to demonstrate a change in patient care. Thus, the basis upon which WES may be publically funded remains vague in the minds of physicians, as there exist various interpretations of what might constitute a change in the management of patient care. On that note, there seemed to be no clear consensus as to what is meant by a change in patient care. Nevertheless, the very aspect of WES that renders it relevant for patients with rare diseases, that is, its capacity to find new disease-causing genes, may be curtailed if public funding of WES was based on a narrow definition of a change in patient management, one focused strictly on treatment.

Theme 3: practical issues for implementing WES into the clinic (practicability)

One aspect regarding the clinical utility of WES, particularly with respect to finding a diagnosis for patients with rare diseases, pertains to some practical concerns that physicians had with this technology. Such concerns were related to the extent to which physicians felt comfortable interpreting results following WES:

So, what do you do with these variable genes with mutations in them or changes in them that nobody really knows if they’re a real mutation or not in a person with no clinical symptoms and then no family history of anything. Then what do you have to do? Do you have to investigate the entire family? I’m not quite sure what the answer to that is. It makes me a bit nervous. … I haven’t really thought about this in great detail at this point. No, maybe it has to be in the context of the family history. Automatically reporting a lot of stuff when you don’t even know what it means can just lead to a lot of extra expenses and concerns and misinterpretations, you know what I mean?

As mentioned by some of the physicians, one of the reasons for this uneasiness and uncertainty relates to the technological limitations in properly capturing gene variability that remain associated with WES:

I still feel though that in order for this to come to clinical practice, the technology has to improve. There is too much variability right now. […] The coverage is so variable that if you don’t find something, it may have nothing to do with the fact of not being there, it just means that it just wasn’t high resolution enough.

Physicians thus expressed doubts as to whether they would be able to interpret results following WES in a suitable amount of time within a clinical context:

If we can resolve some of the timeliness issues and so that the analysis is robust enough that so that we can really be able to use it in a timely manner. If it could replicate, if not do better, than what a targeted gene sequence result would do. If I could get it within eight weeks or something like that, that would be great.

Given the difficulty interpreting results, physicians expressed the need to have access to the proper resources if WES were to be applied to the clinical setting:

We would have to have support, yeah. No question about that. I would have to have somebody… I would have to understand a little bit whether the material’s going to be provided as raw data that I would have to then pass through some filter. Am I going to be given the data? I’ve had some training, but I think I’d have to have a fair amount more training and so would my genetic counselor to undertake that.

The difficulty in interpreting WES results was an important factor in the level of comfort physicians felt in using WES. This sense of unease was compounded by the fact that physicians felt they have little control over what results are fed back to them in the first place
by the clinical laboratories. It may happen that what
the lab reports, or omits to report, to the physician may
have repercussions for making a proper diagnosis for the
patient:

The lab was ... Again, this was a seizure disorder, so the reason
which [name of lab] is not keen on reporting out incidental
stuff – they’re very focused on just answering the question that
was asked. So, yes, propionic acidemia can be a cause of
seizures – and – because exome sequencing is not perfect – it’s
very possible that another mutation could have been missed, right,
so it was important for us to know that so that we could make sure
we had remembered to do organic acids and rule that out. We
already had. So, I did explain to the parents why this was being
reported back to them and what the reasons were.

Presently in Canada, most physicians must refer their
patients to a research study in order to access WES. In
the context of WES research, a conflict ensues
because the purpose of research is to offer generalized
knowledge. The provision of clinically relevant information
goes beyond the scope of research yet, as a
research tool, WES often straddles the line between
research and clinic, a fact that physicians often struggle
with:

Because exome sequencing clinically is not yet available, the
IGNITE Project was kind enough to enroll them in the project,
even though I made it super-clear that the reason why I was
enrolling them is because I didn’t have another option at this
point. It might be a real gene that’s known. It wasn’t necessarily
an unknown gene, but that I had really no option and they were
kind enough to accept that patient. But I’m not sure that’s really
what these projects are for. Right? They’re supposed to be for
when you can’t do clinical testing and you don’t know what gene
it is – in my opinion.

These difficulties reflect how, in providing a diag-
nosis, the already blurry relationship between research
and clinical care that characterizes the field of genetics
intensifies physicians’ doubts over using WES for
diagnostic purposes. The road from research results to
a molecular diagnosis is not a linear process but remains
fluid and potentially subject to change and thus clarification.
Given physicians’ concerns over the interpretation of
results following WES and its potential for finding
disease-causing genes, the clinical utility of WES will
rest on a more clearly defined route between research and
clinical care.

Theme 4: ethical, legal and social issues (acceptability)

With respect to reporting results following WES, the vast
amount of data generated following WES led physicians
to not only question the basis upon which to report results
but also to express the inadequacies of current consent
processes. Traditional consent models are viewed as
ill-adapted for WES. In particular, physicians felt that
patients and their families should be made aware of
the significance of the results and the amount of time
required interpreting them.

But, obviously, the huge challenge for families is to recognize
that with that will come a whole pile of extra, yeah, incidental
findings, some of them significant and some of ... unknown

The clinical utility of whole-exome sequencing

significance. And that the interpretation – the result is easy to
generate – but it’s the interpretation of that that takes time. And
so I think that’s where the consenting process needs to be robust
enough to make families aware of that.

It was also thought that patients and their families
should be made aware of the variability that exists
regarding gene expression. In other words, the view was
that patients need to be told that a gene mutation does
not mean that they have the disease. On that note, it was
also felt that patients be informed as to how confidently
certain diseases can be ruled out following the analysis of
results:

If you say in advance you are going to look for these diseases,
then I think you’re obligated to. If you say you’re not looking for
those diseases, then I can live with that, as long as it’s understood.
It also has to be clear as to how confident those diseases are
ruled out. If we’re not ruling out a BRCA mutation with the same
accuracy as our standard BRCA testing, the patients need to be
aware of that because, if they get breast cancer, I don’t want them
assuming, oh, I’ve already had this checked. Again, that’s an extra
complexity.

As a possible solution to ensuring that patients provide
meaningful consent following WES, physicians considered
providing patients with the possibility to revisit their
results in the future. Possible advancements in knowledge
and evidence in the field of genomics and potential
technological improvements to WES were mentioned as
reasons for which patients should have such an opportu-
nity. A robust, broad and ongoing consent process would
be required. However, at the same time, one physician
questioned the extent to which this could be done in a
clinical setting:

I think most people are going to be a bit uncomfortable with
saying ... and there’s an expectation on the clinician or the
clinical lab to re-evaluate that report or to every two months look
at it again and see if new things come up. I don’t think that’s the
way clinical medicine really works. So, I think the report will be
fixed at a point in time. Now the data may be kept and there may
be ways to formally revisit it. I haven’t really thought about how
that would work, you know, in the sense that if the patient comes
back for another appointment that, instead of actually doing the
experiment again which would cost a lot of money, you formally
reanalyze it. I don’t know. I don’t know how that will work. But
you can see it happening that way. But I don’t think you can ever
say, or that a patient or a physician can assume that this data will
be reanalyzed by the poor lab geneticist every month looking for
new answers. I mean, that ... life doesn’t work that way. You’d
get bogged down and you would never move on.

It is valid to question whether re-analysis or the
re-visiting of results would be feasible given the added
time and cost required in a healthcare system where
resources are already scarce. But how to properly deal
with the practical issues regarding consent procedures
and the return of results was often raised as a common
source of apprehension for physicians. If WES is to be
used as a diagnostic clinical tool, physicians question
how patient autonomy can be protected when faced with
having to interpret and communicate WES results.
In practice, if physicians are uncomfortable or unable
to handle issues of consent and the interpretation or
communication of results appropriately, either other
alternatives to WES will be sought or WES will be used but at the risk of infringing on patients’ rights or unduly expanding physician obligations.

Discussion

The results of our study provide empirical evidence to support the argument in favor of an expanded conceptualization of clinical utility for WES. Many factors come into play when evaluating the use of WES which go beyond the realm of medical or health implications. The different themes elaborated above to elucidate the notion of clinical utility do not exist independent of one another but rather overlap and are often juxtaposed when making clinical decisions. Namely, physicians will need to weigh the added value of providing a diagnosis (e.g. access to health and social services, reducing patient anxiety) against overcoming practical or logistical challenges (e.g. procedural hurdles for funding, the use of limited resources) or the ethical and legal issues that arise in the interpretation or communication of results. As WES moves from research to clinical practice, its progress will be tempered by the challenges that physicians face when deciding whether to use WES. After all, physicians, particularly medical geneticists, will play a primary role in the clinical adoption of WES (12).

It is apparent that physicians’ judgments on utility of WES are viewed in light of local or departmental norms and practices, everyday practice routines and personal or clinical knowledge and experiences. Regardless, an important principle which physicians adhere to is the need to consider the best interest of the patient in deciding the usefulness of WES, a rudimentary concept that often drives clinical decision making. But in evaluating WES, it stands to expand the concept of clinical utility into the personal realm and considers the idea of ‘personal utility’ (13, 14) when contemplating the use of WES. As illustrated in our study, the utility of WES is often framed in regards to the possible overall benefits for the patient, medical or otherwise.

At the same time, physicians expressed concerns that mirror those found in studies focussing on the routinisation of genetic services (15, 16). As Foster et al. (15) write, the challenge lies in maintaining ethical and legal standards while integrating genetic services into clinical practice. If WES is to be used in the clinic, its access should be equitable. However, the way in which public accessibility of genetic services is currently structured around medical rather than psychosocial or personal outcomes, this may likely promote unjust or unequal access. This is often a source of frustration for patients with rare diseases who, after obtaining a diagnosis, will likely not have a change in their treatment plan. Yet, having a diagnosis may relieve years of anxiety and uncertainty for these patients or allow them to access other necessary health or social services.

Another possible source of impediment to the access of genetic services for rare disease patients is physicians’ lack of familiarity and knowledge of rare diseases or genetic technologies, which is highlighted in the results of our study. Whether or not a clinician will have the opportunity to provide a clear diagnosis to a patient thus still depends on the judgment of other healthcare professionals and their own medical knowledge of rare diseases. Thus the lack of familiarity with rare diseases, and not just genetic testing, underlines how WES may be clinically useful only to the extent that healthcare professionals are familiar with rare diseases as well as genetic testing. Therefore, physicians should be equipped with proper education and training so that they are up-to-date with rapidly expanding genetic advancements. Having the proper knowledge will also allow the physicians to filter through genomic data and present it in a way that is meaningful and timely for the patients. The complexity of WES testing and its results must be reflected in the consent process to ensure patient autonomy through informed decision making. As such, new models of consent are needed, and standards regarding the communication of WES results should be elaborated for physicians and clinical laboratories.

Once the practical and technical challenges of WES are resolved, physicians agree that WES will establish a certain role in medical care. How physicians quantify this role will be dependent on whether WES offers added value to clinical practice or whether it provides just another set of data; this will have implications on whether WES will be used to replace traditional diagnostic methods or resorted to only as a complementary tool. Nevertheless, what is observed in the medical profession is the way in which WES has influenced a paradigm shift in how physicians analyze patient management and how they deal with the provision of diagnoses.

For rare diseases, building a case for the use of WES to procure a diagnosis is relatively straightforward with the benefits most likely outweighing the drawbacks. But nuances on the utility of WES may change when WES is applied in the context of common diseases or as a screening tool for preventive care. Although our study was limited on the perspectives of physicians, it would also be interesting to compare the viewpoints of different stakeholders (e.g. patients, laboratory personnel, genetic counselors, nurses, policy-makers and public health professionals). Drawing on and comparing different perspectives would enlighten the debate on the clinical utility of WES and provide a comprehensive outlook on the implementation of WES into mainstream medical practice.

Limitations of the study

While this study provided clarifications as to how physicians view the clinical utility of WES, particularly with respect to patients with rare diseases, certain limitations characterize this study. One possible limitation relates to the use of triangulation. Given the disadvantages associated with triangulation (17), resorting to triangulation would not have necessarily added any information to our study.
Acknowledgements

This work was performed under the Care4Rare Canada Consortium funded by Genome Canada, the Canadian Institutes of Health Research, the Ontario Genomics Institute, Ontario Research Fund, Genome Quebec, and Children’s Hospital of Eastern Ontario Foundation. We would also like to thank Daphne Esquivel Sada, Bartha Knoppers, Nicole Palmour (Centre of Genomics and Policy, McGill University) and Karen MacDonald (University of Calgary) for their contribution and comments to earlier versions of this manuscript.

References

1. Iglesias A, Anyane-Yeboa K, Wynn J et al. The usefulness of whole-exome sequencing in routine clinical practice. Genet Med 2014: 16 (12): 922–931.
2. Beaulieu CL, Majewski J, Schwartzentruber J et al. FORGE Canada Consortium: outcomes of a 2-year National Rare-Disease Gene-Discovery Project. Am J Hum Genet 2014: 94 (6): 809–817.
3. Yang Y, Muzny DM, Reid JG et al. Clinical whole-exome sequencing for the diagnosis of mendelian disorders. N Engl J Med 2013: 369 (16): 1502–1511.
4. Rossolatos D, Aitchison KJ. Genomics for clinical utility: the future is near. Genome Med 2014: 6 (1): 1–3.
5. Grosse SD, Khoury MJ. What is the clinical utility of genetic testing? Genet Med 2006: 8 (7): 448–450.

The clinical utility of whole-exome sequencing

6. Burke W, Laberge AM, Press N. Debating clinical utility. Public Health Genomics 2010: 13 (4): 215–223.
7. Smart A. A multi-dimensional model of clinical utility. Int J Qual Health Care 2006: 18 (5): 377–382.
8. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006: 3 (2): 77–101.
9. Fereday J, Muir-Cochrane E. Demonstrating rigor using thematic analysis: a hybrid approach of inductive and deductive coding and theme development. Int J Qual Methods 2006: 5 (1): 1–11.
10. Bowen GA. Naturalistic inquiry and the saturation concept: a research note. Qual Res 2008: 8 (1): 137–152.
11. Guest G. How many interviews are enough? an experiment with data saturation and variability. Field Methods 2006: 18 (1): 59–82.
12. Boycott KM, Vanstone MR, Bulman DE, MacKenzie AE. Rare-disease genetics in the era of next-generation sequencing: discovery to translation. Nat Rev Genet 2013: 14 (10): 681–691.
13. Foster MW, Mulvihill JJ, Sharp RR. Evaluating the utility of personal genomic information. Genet Med 2009: 11 (8): 570–574.
14. Grosse SD, McBride CM, Evans JP, Khoury MJ. Personal utility and genomic information: look before you leap. Genet Med 2009: 11 (8): 575–576.
15. Foster MW, Royal CD, Sharp RR. The routinisation of genomics and genetics: implications for ethical practices. J Med Ethics 2006: 32 (11): 635–638.
16. Schmitz D. Exceptional know how? Possible pitfalls of routinising genetic services. J Med Ethics 2010: 36 (9): 529–533.
17. Thurmond VA. The point of triangulation. J Nurs Scholarsh 2001: 33 (3): 253–258.