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ORIGINAL ARTICLE

Genetic health professionals' experiences with initiating reanalysis of genomic sequence data

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Abstract

Despite the increased diagnostic yield associated with genomic sequencing (GS), a sizable proportion of patients do not receive a genetic diagnosis at the time of the initial GS analysis. Systematic data reanalysis leads to considerable increases in genetic diagnosis rates yet is time intensive and leads to questions of feasibility. Few policies address whether laboratories have a duty to reanalyse and it is unclear how this impacts clinical practice. To address this, we interviewed 31 genetic health professionals (GHPs) across Europe, Australia and Canada about their experiences with data reanalysis and variant reinterpretation practices after requesting GS for their patients. GHPs described a range of processes required to initiate reanalysis of GS data for their patients and often practices involved a combination of reanalysis initiation methods. The most common mechanism for reanalysis was a patient-initiated model, where they instruct patients to return to the genetic service for clinical reassessment after a period of time or if new information comes to light. Yet several GHPs expressed concerns about patients' inabilities to understand the need to return to trigger reanalysis, or advocate for themselves, which may exacerbate health inequities. Regardless of the reanalysis initiation model that a genetic service adopts, patients' and clinicians' roles and responsibilities need to be clearly outlined so patients do not miss the opportunity to receive ongoing information about their genetic diagnosis. This requires consensus on the delineation of these roles for clinicians and laboratories to ensure clear pathways for reanalysis and reinterpretation to be performed to improve patient care.

Keywords Next generation sequencing · Genetic counselling · Bioethics · Reanalysis · Variants of uncertain significance

Introduction

Translating the power of genomic sequencing (GS) using next generation sequencing technologies from the research context into clinical care is currently one of the major goals of researchers and health-care providers, particularly in areas such as rare disease and inherited cancers [1]. This is leading to tangible benefits for patients, such as increases in diagnostic yield for genetic disease compared to 'standard' sequencing methods. Depending on the patient cohort under investigation, the selection criteria used, and the type of GS employed (e.g. exome, genome, or condition-specific gene panels), studies are reporting rates of 12–68% [2–9], although this will continue to change as the technology evolves. Despite this success, clearly there remains a sizable proportion of patients for whom a genetic cause has not yet been identified at the time of the initial GS analysis (although some of these cases may not have a genetic basis to their condition).

As more patients and research participants are sequenced, our knowledge base of which variants are and are not pathogenic increases. This is through the identification of both new genes associated with particular conditions and also new variants in genes previously reported. Although this means that the 'hit rate' of newly sequenced samples should increase, it can only help previously sequenced patients if samples are reanalysed. The term reanalysis refers to the process where

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laboratories re-run previously analysed GS data through a new version of their bioinformatic pipeline to check for new potentially causative variants. This is in contrast to reinterpretation where a list of variants identified during the initial analysis are re-curated to check for updated evidence of pathogenicity for these variants. Reinterpretation of previously identified variants where the significance is unclear (variants of uncertain significance; VUS) has been shown to clarify variant classifications and assist clinical decision making in patients with hereditary cancers [10].

A number of research and clinical groups have recently undertaken systematic reanalysis of their previously sequenced samples. These have shown considerable success with reanalysis leading to genetic diagnosis rates increasing between 4 and 32%, in some cases as soon as 12 months following the initial analysis [11–19]. While this suggests that routine reanalysis would end the diagnostic odyssey for many patients, the additional time that this process would involve is not insignificant and leads to questions of feasibility, particularly if there was no additional charge. It also raises the question of who should initiate reanalysis of a patient sample; should this be the laboratory, the clinician, or the patient (via the clinician)? Confusion over stakeholder roles and responsibilities is reflected in the process of obtaining consent to undertake reanalysis or reinterpretation of existing data. Indeed, a study done in 2018 of 58 consent forms used in diagnostic GS showed that 25 (43%) did not even mention the possibility of data reanalysis or variant reinterpretation [20]. Of the 21 forms that explicitly mentioned reinterpretation for clinical purposes, there was considerable variation regarding with whom the responsibility for initiating this process resided. Ten forms suggested that the laboratory will initiate any subsequent variant reinterpretation, six indicated that reinterpretation must be initiated by the clinician, and five left this process in the hands of the patient [20]. These findings highlighted concerns regarding abdication of responsibility by laboratories and clinicians, as well as patients' abilities to advocate for themselves. It was also unclear how this was being translated into clinical practice.

To address this question, we sought to interview clinical geneticists and genetic counsellors across Europe, Australia and Canada about their experiences with data reanalysis and variant reinterpretation practices following requests for GS in their patients. This follows on from interviews conducted with laboratory personnel conducted across these regions which investigated the current practices and challenges experienced by laboratories performing diagnostic GS [21, 22].

Methods

Qualitative methods were used to explore the views and practices of genetic health professionals (GHPs) with regards to reanalysis of patients' genomic sequence data. GHPs were recruited using a purposive sampling strategy to identify both genetic counsellors and clinical geneticists who request different types of GS technologies (including targeted large gene panels, exome and genome sequencing) for patients, primarily in the diagnostic setting. Potential participants were identified using internet searches to find relevant genetic services, and snowball sampling. Interviews were semi-structured in nature and were conducted by one member of the research team (DV). These interviews explored a range of different topics relating GHPs' GS requests, including the types of patients for whom they request testing, and which results they receive from laboratories. Here we report data from the interviews focussing on reanalysis/reinterpretation practices and views. Interviews were audio-recorded, transcribed verbatim and analysed using inductive content analysis in which content categories were derived from the data, rather than pre-determined [23–25]. Each transcript was coded into broad content categories. Sections of the data within the broad categories were compared and more specific subcategories were developed. All interviews were coded by DV; KS and PB coded a subset to confirm the coding scheme.

This study was approved by the SMEC Review Board (Social and Societal Ethics Committee), KU Leuven and by the Research Ethics Board of the Faculty of Medicine, McGill University.

Results

Participant characteristics

Thirty interviews were conducted with 31 GHPs (24 clinical geneticists and 7 genetic counsellors), which included participants from 30 different institutions in Europe (15), Australia (10), and Canada (5). One interview was conducted with two GHPs from the same institution. Participants had a mean of 9.5 years (1–30 years) experience in their current role and a mean of 14.3 years (3.5–38 years) experience in the field of genetics. Of these participants, eight were involved in the analysis and interpretation of GS data as part of their role and an additional nine assist with patient review at multidisciplinary team (MDT) or other types meetings with their local laboratory.

GS data reanalysis practices and views

GHPs described a range of different practices relating to processes required in order to initiate reanalysis of GS data for their patients. They also discussed their views about how effective their current processes are and what they think might be more appropriate. We have presented these views and practices identified within the clinical context by

initiation model type: (1) patient-initiated model, (2) laboratory-initiated model, (3) clinician-initiated model.

Patient-initiated model

The most commonly discussed mechanism for reanalysis was on the initiative of the patients (via the GHP). Participants described how, if the cause had not been identified during the initial analysis, they would tell patients that they should return to the genetic service for clinical reassessment after a certain period of time. This ranged from anywhere between 1 and 5 years, depending on the GHP, and may require a new referral from their primary health care physician.

> If we don't have a certain positive finding, we say that we might have new information in one, or two, or three years. So, please get back to us if you still want us to take this further. So, we would need some kind of referral to do the analysis.
>
> Participant 4, clinical geneticist

> We will say to patients that, at this point in time, this is negative. Or at this point in time it's a VUS and we can't go any further than this but please come and see us again in 12 months' time and we'll see what's available to you. So, that kind of triggers then for the clinician or the counsellor involved to then contact the lab in 12 months' time, when the patient re-presents or comes back for an appointment, that we would then, in preparation for that, contact the lab to see if anything new has happened.
>
> Participant 14, genetic counsellor

GHPs may also encourage patients to return for reassessment if new information comes to light, such as changes in symptoms, disease progression, a newly affected family member, or if they are planning a pregnancy.

> What we tell our patients is, if there's significant changes to your personal history or family history, get in contact with us to see whether reanalysis is needed.
>
> Participant 17, clinical geneticist

Several GHPs mentioned that, if a patient does not have a diagnosis, rather than being discharged from care and relying on the patient to initiate contact for reanalysis, they have a system where the patient is booked in for another appointment.

> We schedule review appointments. So, we don't discharge people that we think still have a monogenic disorder in a negative exome… That's our prompt, really, to revisit the situation.
>
> Participant 16, clinical geneticist

Several GHPs expressed concerns regarding leaving initiation of reanalysis in the hands of the patients. In some cases, this was because they were worried patients would not understand that they needed to recontact the clinician for reanalysis to occur. For others, they were concerned that only the more motivated patients/parents will initiate reanalysis, which may exacerbate health inequities, or that patients are lost to follow-up.

> I think it does [work] for certain families but I worry about other families that maybe are not so active [about their healthcare]… I do worry about people falling off the radar. What about when kids grow up and, you know, there's just so much stuff that can happen in a family. What if a parent dies and they were the only one that knew about it and just all of that. I just find that really problematic.
>
> Participant 14, genetic counsellor

Others were not concerned that patients do not understand or may forget to initiate reanalysis because they ensure that the letter they send to patients after the consultation explains this.

> Well, I don't make a fixed appointment already for 2, 3 years. I leave it a bit up to them. But I write in my letter that it's good to see them back…But I have the impression that if you explain well and you provide good service that they come back…And they understand that there is still a lot that we don't know or that we miss.
>
> Participant 29, clinical geneticist

A couple of participants cited the fact that patients had returned for reassessment as an indicator that the patient-initiated system was working.

> For example, there were many reports issued already of course and, when counselled, many patients were counselled, and they really do kind of come back in a year, a year and a half, you know, if there is something new about their VUS, [to ask] 'can we now maybe classify it to the benign or the pathogenic pole'?
>
> Participant 5, clinical geneticist

A small number of GHPs cited experiences where patients had been grateful to receive new classification or new diagnosis following reanalysis. However, it was highlighted that not everyone still wants to receive a diagnosis down the track, particularly if their child has died and they are not planning to expand their family further. In fact, a proportion of GHPs felt that leaving the responsibility to initiate reanalysis with the patients meant that only those who were motivated enough to return would have their sample reanalysed, ensuring that resources were being used to assist those who were definitely still interested in receiving a diagnosis.

> For me it works quite well because I see that people who are really still seeking for results, for a diagnosis, for example, if they still want to have a child or if they have family members that [are planning] pregnancies. Or if, for example, the disorder of the child becomes worse or changes in time, then those people certainly are motivated to come back. I also have patients that sometimes, when I recontacted them, are less interested in follow up.
>
> Participant 3, clinical geneticist

One participant felt that one of the major issues (and drivers for the patient-initiation model) was a general reluctance by all parties to take responsibility for reanalysis and recontact processes, which was highly influenced by workload pressures.

> I think what's been really difficult about that is that nobody wants to take ownership of whose responsibility it is to initiate that. So, certainly the labs are overwhelmed. They're overworked. They don't feel that they've got the capacity to go back and reanalyse variants. And, as a clinic, we feel the same. We don't have the capacity to keep lists of people that we want to review variants.
>
> Participant 18, genetic counsellor

Yet, a proportion of participants felt that it was inappropriate for patients to initiate reanalysis. This was because patients do not have the knowledge and expertise to know at which point further analysis would be appropriate, and because it can place families under additional pressure.

> I think that puts a lot of pressure on the families and relies on families who may be better at advocating for themselves or thinking through those kinds of issues. Or maybe families for whom this is more valuable intrinsic information. But is that equitable? I don't know.
>
> Participant 20, genetic counsellor

Laboratory-initiated model

When asked, a large proportion of the GHPs indicated that, to their knowledge, the laboratories from which they requested GS did not currently have routine or systematic reanalysis procedures in operation. Reanalysis would need to be triggered by a clinician which may or may not involve an additional fee, depending in the laboratory in question.

Yet, some of the GHPs stated that the laboratories they engage with do have systems in place to perform some degree of reanalysis or reinterpretation. This usually involved bioinformatic reassessment of identified variants, which involves updates of databases and detection software to reassess the pathogenicity of variants, or by a reinterpretation of the variant in response to a 'hit' using a database, such as GeneMatcher.

> If there are, let's say, multiple patients, or also people having variants in the same gene with the similar phenotype internally, or we hear something new after we put the data in a database, such as GeneMatcher… If I get matches and I see that the phenotype is comparable, then I go back to the patients. I contact them again and tell them "Look, we are a little bit further. Do you agree that we discuss how far we come and that maybe we do additional investigations?".
>
> Participant 3, clinical geneticist

Several GHPs mentioned that the implementation of laboratory-initiated processes had meant that they needed to change consent forms and processes to include information about the possibility for patients to be recontacted with new information.

> But for the organization internally, we had to really work on the consent form and information that we had to put it in. First it was not in there and then you get a reanalysis result and you didn't ask for it. Of course, as a clinician you had to cope with that. So now it's all within the information beforehand so that the patient knows.
>
> Participant 10, clinical geneticist

However, participants clarified that none of these laboratories rely solely on laboratory-initiated processes and it was common for reanalysis practices to comprise a mix of two or more initiation mechanisms.

In contrast to those who supported a patient-initiated approach for reanalysis, a proportion of the participants interviewed suggested that a laboratory-initiated periodic or ongoing reanalysis process would be the best situation. This was for several reasons, including that having clinicians initiate reanalysis created an extra step in the process.

> This isn't me handing it off from a clinical point of view. It probably needs to be from a laboratory point of view because otherwise it's clinical people having to go back to a laboratory again… It's an added step. So, it really needs to be integrated into laboratories that are doing a lot of analysis that perhaps there is a system for recall of previous results.
>
> Participant 24, genetic counsellor

Yet even those who considered a laboratory-initiated model to be the ideal situation acknowledged that, for many laboratories, this was not feasible given current available funding and resources.

> Yes, as I said to our lab, we would love it if all the data from every NGS [next-generation sequencing] test got

> reviewed every 5 years…and with a report sent back to the clinicians. That would be just beautiful. But it's not going to happen.
>
> Participant 15, clinical geneticist

> I think both the laboratory and the clinical services are definitely feeling the responsibility of reanalysis and are wishing that we could provide that service… However, when you have waiting times and lag times to getting results the way that we have, I don't think we can justify it just yet when we can't even get the primary test reports out within a particular time frame. So, there are greater things to take care of before we start addressing that question, even though it does bug us.
>
> Participant 19, genetic counsellor

Several GHPs described models with different combinations of reanalysis initiation mechanisms. One common approach involved a combination of laboratory- and patient-driven triggers. In this approach, while the GHP would tell the patient to return, either after a set time period or because of a change of situation (as described above), the laboratory would also contact the clinician if there had been a reclassification of a variant.

> We now tell [the patient] if there is…nothing found now, we always say, 'well, there can be done an update in the software and then sometimes results come forward that are not seen now. So that may be the case and if you're OK with that, we recall you back'. With [variants of] uncertain significance, we always tell them, 'please enquire in a year, or in two years, to ask whether there is any additional information'.
>
> Participant 9, clinical geneticist

Clinician-initiated model

None of the GHPs interviewed indicated that they operated in a system that relied solely on the clinician to initiate a reanalysis for their patients. A few of the GHPs described an approach which, in addition to both laboratory- and patient-initiated reanalysis incorporated scheduling of follow-up appointments for patients. Other participants described models in which the clinicians (or, in one case, the clinic staff) also kept track of the suspicious variants in their patients and periodically reassess the patients over time.

> I have a secretary. I have a recall system. I don't know how she manages it exactly, but it seems to work really well. I guess things go into some kind of computer program calendar that just pulls things up, 'cos every month I get a pile of charts outside my office being like, these are the ones you wanted to look at again.
>
> Participant 23, clinical geneticist

A number of GHPs explained that the decision between taking responsibility for triggering reanalysis by recontacting or leaving it in the hands of the patients depends on how likely they think the VUS identified will be the cause of the condition.

> Well, it depends a bit on how likely I think it is that a variant is disease-causing. Sometimes it is very likely that it will turn out to be disease-causing and then I've a bit more active approach than when I think that's unlikely. Then I leave it to the parents to recontact us when they feel like it and I usually propose, well, in about 2 or 3 years.
>
> Participant 7, clinical geneticist

However, it is not possible for all patients to be re-reviewed regularly in all genetic services and one clinical geneticist queried the use of resources in doing so.

> It is one of the areas of difficulty that we are trying to address in our model of care because we all like to follow our patients if they're undiagnosed, or even if they are diagnosed. But then when you look at the wait time for new assessments and you only have a limited number of geneticists you wonder whether that's the best utilisation of resources to concentrate on. Patients we have seen three, four times and we still don't have a diagnosis? Or see new patients that need a fresh set of eyes to see them!
>
> Participant 26, clinical geneticist

Although some GHPs implied that their current combination of reanalysis processes seemed to be working to a degree, others felt that they needed to wait to see how well the system worked over time. One participant who explained that, until recently, their system had been quite haphazard, was in the process of implementing a more systematic approach.

> Well, I don't think it is working very efficiently. But that is why we start this department-wide novel procedure around this reanalysis that is more formalized and how frequently it is done and what is [done]. Because [currently] it depends on the doctor and on the parents if it's done more specifically. So, it should be done routinely, and it should be counselled, also routinely, to the parents.
>
> Participant 9, clinical geneticist

Finally, several GHPs suggested a role for primary healthcare providers in sharing the responsibility with patients to refer their patients for reassessment when sufficient time has passed.

> And then I guess the referring doctors, or the caring physicians who look after the families will also receive letters that are sent to patients where the onus is put

back on them. So, the onus is not just on the patient. It's about the caring physicians as well because they have that information on file within the letters.

Participant 19, genetic counsellor

Discussion

To our knowledge, this is the first study that specifically addresses GHPs experiences and views on initiating reanalysis processes following GS in their patients. Others have used interviews and surveys to investigate recontact procedures and shown that although not all practitioners recontact patients in response to new information, when they do it is far from systematic [26–29]. However, recontact is a very broad term that encompasses many different situations, including (but not limited to) contact to inform of new genetic tests that could be of benefit to former patients and recontact as part of a research study [26]. While patients may be recontacted if variant reinterpretation takes place, the decision whether to reanalyse, how frequently, and how this is initiated, involves different choices and competing factors compared to whether or not, and by whom patients should be recontacted in response to new information. In addition, recontact technically only refers to situations where the patient has been discharged from care [30], which may not apply to some patients who remain undiagnosed (and for whom reanalysis may be applicable). For these reasons, we think it is important not to conflate the two processes. Therefore, our study elucidating the practices around reanalysis provides an important and novel contribution.

Our findings show a diverse range of practices regarding the initiation of reanalysis following GS, with participants often describing a combination of patient-, clinician-, and laboratory-initiated reanalysis practices. This lack of a consistent model reflects the diversity seen in studies that have explored experiences of health professionals with patient recontact [26–29].

In our study, we identified that the most common model for initiation of reanalysis was for GHPs to tell their patients to return to the clinic in order to check for updates, either after a set time period, or in response to new clinical information in themselves or their family. Some of our participants felt that, anecdotally, this system was working quite well and that patients were returning. This was more likely if the undiagnosed patients were booked in for repeat appointments, rather than discharged, as was the case with a small number of the GHPs. Yet others raised questions around patients' abilities to proactively request this service. This could be due to their lack of understanding of what a negative result might mean or because it places additional pressure on patients or families to remember to return when they are already dealing with a complex medical situation. And while a new symptom or affected family member might trigger patients (or parents) to contact their clinician, encouraging patients to return after two, three, or five years may lead to situations where only the more educated or persistent families will access reanalysis, which could exacerbate existing health inequities [26, 27]. Clearly, whether it is appropriate to rely on a patient (or their parent) to initiate reanalysis or reinterpretation is very patient- and context-specific and clinicians will need to use their clinical judgement to determine to what degree to do so. However, there needs to be acknowledgement that relying solely on this mechanism may be unreliable in some instances.

In contrast, some GHPs felt that adding instructions concerning when to return to the genetic service in the patient letter combated this sufficiently, both because the patient could re-read it after the appointment and also because it would alert their general practitioner or family doctor to this option. In fact, some GHPs proposed that these primary care physicians should take at least partial responsibility for encouraging the patient to initiate reanalysis. While on the one hand this would make sense because the patient would require another referral to the genetics service, it would also require GPs to a) appreciate that a negative result does not rule out a genetic cause, and b) develop some kind of reminder system to alert either themselves or their patients that sufficient time had passed to warrant reanalysis. This is then likely to lead to similar problems encountered by most of the GHPs who do not feel that they have the capacity or systems in place to keep track of their undiagnosed patients in order to take responsibility for triggering a reanalysis process.

Several GHPs described using their clinical judgment about how likely they think the VUS identified is to be the cause of the condition to make decisions on whether to follow up the patient or leave it in their hands to initiate the reanalysis. While this approach may be adequate for experienced GHPs, it may be less so for health professionals who have little (or no) genetics training and who are unable to assess the likelihood of pathogenicity based on laboratory reports. This will only be exacerbated as genetics becomes more integrated into other medical specialties, such as neurology, nephrology, etc. Therefore, it is important to have systems in places so that all patients can have access to reanalysis when appropriate, regardless of their referring clinician. However, this reanalysis should always include input from a clinician with genetics experience.

While a proportion of the GHPs felt that a routine reanalysis process initiated by the laboratory would be ideal, many acknowledged that the technology to make this a reality was not yet available and current systems which relied on manual curation of identified variants meant that this was not yet feasible, as suggested by others [26]. However, some laboratories do seem to have procedures in place for reassessment of identified variants and there are reports in the

literature of automated systems for the reanalysis of clinical exome data with good results [31]. Although technological advancements may assist in the laboratory components associated with reanalysis and variant reinterpretation, the role of the experienced clinician to determine which patients may benefit most, depending on their clinical picture and how thorough the initial analysis way, should still be integrated into the process in some way. Importantly, the roles and responsibilities of each of the parties involved should be clearly delineated and the patient should be made aware of these.

While implementation of automated systems may be a way to address some of the issues around workload, they do not address concerns raised that some patients may no longer desire an answer for their genetic condition, a situation that may arise, for example, once a child has died. One suggestion as to how this could be averted would be to implement a 'dynamic consent' process, whereby the consent form is located online and the patient (or parent) has the option to check a box indicating whether they would like ongoing reanalysis to identify the cause of their condition. If not, their data could be excluded from ongoing automated processes. They could also change their preference if their preference or situation changes.

While the exploratory nature of our study does not lend itself to generalisability, it provides key insights into the challenges associated with reanalysis procedures from the perspectives of clinicians who are requesting GS for their patients. We chose to only sample participants from across Europe, Australia and Canada as a follow on from interviews conducted with laboratory personnel conducted across these regions [21, 22] which means we cannot comment on the experiences of GHPs practicing in other parts of the world. We have also deliberately focused exclusively on reanalysis in the clinical context, rather than in research. This distinction is important because the primary goal of diagnostic GS is to identify a diagnosis with the hope of improving patient care, which then entails a professional duty of care to the patient on behalf of the GHP. This is in contrast to the research setting where the primary goal of the testing is to generate knowledge (although improvements in patient care may be a secondary goal).

There is currently no legal duty for laboratories to reanalyse data [32]. However, the fact that reanalysis of previously undiagnosed patients can lead to diagnostic yields ranging from 4 to 32% depending on the cohort, time since initial analysis, and the degree of manual curation undertaken [11–19], which could potentially change treatment or management, suggests that there might be good reasons to integrate this into routine practice. However, this should only be done with the knowledge and consent of the patient (or their parent/guardian), which should be sought as part of the initial pre-test counselling process. Regardless of the reanalysis initiation model that is eventually adopted by a genetic service or clinic, consent forms should mention the possibility for data reanalysis or variant reinterpretation, and also clearly outline the roles and responsibilities of the patient and clinician so that those who want to receive ongoing information about their genetic diagnosis will not miss the opportunity to do so. For this to occur, we require consensus on the delineation of these roles for clinicians and laboratories to ensure clear pathways for reanalysis and reinterpretation to be performed to improve patient care.

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