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Exploration of genetic health professional - laboratory specialist interactions in diagnostic genomic sequencing

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Running title: Experiences returning sequencing results

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Abstract

Like any new technology, rapid integration of genomic sequencing (GS) into the clinical setting can pose challenges for genetic health professionals (GHPs) using it to diagnose patients. We conducted semi-structured interviews with 31 clinical geneticists and genetic counselors across Europe, Australia and Canada to gain a better understanding of the issues they were experiencing when requesting GS and receiving reports from laboratories. There was a spectrum of interactions between genetic health professionals and laboratories. This ranged from those that almost exclusively request sequencing from the laboratory that is affiliated with their genetic service, to those who do not have access to exome sequencing 'in-house' and instead send patient samples to a selection of different external laboratories. In general, a closer interaction between the clinicians and the laboratory scientists increased the involvement of the clinicians in the analysis/interpretation process. This appeared to lead to fewer, but more clinically relevant variants being reported, and greater GHP satisfaction in what is reported. Our findings suggest that GHPs consider integration of clinical expertise into the analysis/interpretation process is critical to ensure that the variants reported are of high clinical significance to patients. They also highlight the importance of providing GHPs with training in report interpretation.

Keywords: next generation sequencing; genetic counseling; bioethics; incidental findings; unsolicited findings; variants of uncertain significance

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Introduction

Integration of genomic sequencing (GS) into the field of medicine is increasing the rate of identification of genetic causes of disease across a range of clinical settings (Soden et al., 2014; Stark et al., 2018; Yang et al., 2014). By decreasing the time to diagnosis, this is reducing the use of unnecessary (and at times, invasive) tests and improving overall patient care (Stark et al., 2018). Yet, as we have seen with the introduction of many new technologies, GS also carries with it a range of challenges, some of which are unique and others that are merely exacerbations of existing issues. A number of challenges have been highlighted in a US-based study of genetic health professionals (GHPs) returning results from GS in the research setting (Wynn et al., 2018). These include issues relating to the greater length of time required to return results from GS to patient-participants, variation in what was discussed and the support materials used in the disclosure session, and handling patient-participant responses to receiving different types of results, including positive and negative findings, secondary findings (ie, where disease causing variants unrelated to the clinical question are actively sought), and variants of uncertain significance (VUS).

However, to our knowledge, there has been little exploration of GHPs experiences with requesting GS from laboratories and subsequently receiving reports for their patients. Given that GS encompasses a range of different technologies (including small or large condition-specific panels, exome or genome sequencing), and GHPs may have access to testing from a number of different laboratories, it is relevant to investigate how GHPs make decisions about which types of tests they request and from whom. The nature of the testing, particularly with exome or genome-wide analysis, increases the potential for identification of both VUS and also unsolicited findings (UF), where disease-causing variants unrelated to the clinical question are identified inadvertently during the analysis, compared to previous

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sequencing methods. This fact, in addition to concerns raised by laboratory personnel in a previous study that some clinicians fail to fully appreciate the significance (or lack thereof) of VUS (D. F. Vears, K. Sénécal, & P. Borry, 2017), suggest a need to explore how GHPs are dealing with receiving reports from GS. To address these questions, we sought to interview clinical geneticists and genetic counselors about their experiences requesting GS and receiving reports from laboratories. The aim of this study was to explore the ways in which GS was influencing their practice and any challenges they were experiencing due to the implementation of this technology in their practice.

Methods

Qualitative methods were used to explore the experiences of genetic health professionals requesting genomic sequencing for patients. Genetic health professionals were recruited using a purposive sampling strategy to identify both genetic counselors and clinical geneticists who request different types of genomic sequencing technologies, including targeted large and small gene panels, exome and genome sequencing for patients, primarily in the diagnostic setting. We sampled participants from across Europe, Australia and Canada as a follow on from interviews conducted with laboratory personnel conducted across these regions (D.F Vears, K. Sénécal, & P. Borry, 2017; D. F. Vears et al., 2017). Sampling aimed to recruit participants with representation across different countries (within Europe) and States/Provinces (within Australia and Canada), yet also enrich for services known to have considerable experience with offering GS to patients (as identified through our previous research with laboratory specialists). To achieve this, potential participants were identified using three strategies: 1) internet searches to identify genetic services - potential participants were approached via email if the researcher (DV) gauged from their online profile that they were offering GS to patients; 2) snowball sampling – GHPs were asked to suggest other potential participants at the completion of their interview; 3) participants from a previous study of laboratory personnel (D. F. Vears et al., 2017) were asked to suggest GHPs that they knew of offering GS to patients. While we attempted to recruit more

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genetic counsellors, we were restricted by the number of counsellors who were able to request GS for patients, particularly in Australia and parts of Europe.

Interviews were semi-structured in nature and were conducted by one member of the research team (DV), either face-to-face or by telephone depending on the location and preference of the participant. These interviews explored a range of different topics relating to their genomic sequencing requests, including the types of patients for whom they request testing, which tests they request, and which results they receive from laboratories. Here we report data from the interviews focussing on the interactions between the GHPs and the laboratory scientists and on the satisfaction of the former with the results that are reported to them by the latter. Interviews were audio-recorded, transcribed verbatim and analyzed using inductive content analysis in which content categories were derived from the data, rather than pre-determined (Downe-Wamboldt, 1992; Graneheim & Lundman, 2004; Schamber, 2000). 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-one interviews were conducted with 30 GHPs (24 clinical geneticists and 7 genetic counselors), which included participants from 30 different institutions in Europe (15), Australia (10), and Canada (5). 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

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genomic sequencing 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.

Genetic health professionals' interactions with laboratories

There was a spectrum of interactions between genetic health professionals and laboratories. This ranged from those that almost exclusively request sequencing from the laboratory that is affiliated with their genetic service, to those who do not have access to exome sequencing 'in-house' and instead send patient samples to a selection of different external laboratories. The former was quite commonly depicted by the European GHPs that we interviewed and the latter more so by Canadian GHPs in our sample, with the Australian participants less tied to either model. These request models had their own benefits and challenges, particularly in relation to the GHPs' degree of involvement in the analysis and interpretation process, their decision-making regarding which laboratories to use (when they have a choice), and their level of satisfaction with what is reported.

Involvement in the analysis and interpretation process

On the one hand, the GHPs that send the majority of their patients' samples for testing to an in-house testing service often described a very close working relationship with the laboratory scientists who are responsible for data analysis. This was often enhanced by their close proximity; many described that the people analysing the data were often in the same building or just down the road. This proximity led to easy channels of communication between the GHPs and laboratory scientists.

There is short distance for discussing things, both direct and indirect. [There is] at least one weekly meeting with each other but there's often informal meetings in between, by email or telephone, or just to walk on by, because the lab is also nearby. So, there's a tight relationship I must say.

Participant 9, Clinical Geneticist

Many of the clinicians interviewed were also either involved in aspects of the analysis/interpretation process as part of their role or participated in regular MDTs, where

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GHPs, laboratory scientists, and sometimes other referring clinicians would discuss patients in whom sequencing had been performed in order to better determine which variants are most relevant to the patient's phenotype. While some centres discuss all patients that undergo sequencing, others just discuss the complex cases.

We have these meetings once every month where we discuss, well not the clear-cut cases. Of course, there are some results that are just clear-cut and there's no doubt about the pathogenicity of the variants but there are also a lot of variants that are not that clear-cut and they are all discussed during those meetings.

Participant 30, Clinical Geneticist

For some, these MDTs can also be a platform for ongoing negotiations and development of policies to improve the service.

And just because of the construction that we have built up, these multidisciplinary expertise meetings, we continue to negotiate and to adapt the way we think it is best, and the way it works best for our department and our group.

Participant 3, Clinical Geneticist

During the meetings, GHPs often learn which variants have been identified prior to receiving a formal report. They described their role in deciding which variants would/would not make it onto the report based on the variant's relevance to the patient's phenotype. They stressed the importance of the interaction between the laboratory scientists and clinicians in this process and how the presence of clinicians at these meetings allows for the exchange of important phenotypic information additional to that provided with the initial referral.

Yes, [it's] really very, very important to have this meeting because we all together decide that the variant is the cause of the disease. And sometimes the laboratory is not sure, and the clinician can say, "yes, it's a good candidate and we agree it's the cause of the disease". And sometimes the clinician can say, "well, your stop variant, for example, is not coherent with the clinical feature so we don't agree that this is the cause of the disease".

Participant 28, Clinical Geneticist

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On the other hand, some genetic health professionals almost exclusively send their patients' samples to external laboratories for testing and therefore do not share the same proximity to the laboratories analysing the data of their patients. When this is the case, the participants described how practices and services provided vary from laboratory to laboratory, each with their own positive and negative aspects.

So, I guess I could divide them into two big categories. There are the labs that are more clinically oriented and have probably better services in terms of interpretation and are less driven by the technology but more by the making a diagnosis. And some other labs usually tend to have larger panels and have the newer genes more quickly and are more driven by the technology but sometimes their interpretation is not as strong as we would like or as helpful as we would like.

Participant 25, Clinical Geneticist

Participants reported additional challenges working with various laboratories, such as being required to use different requisition and consent forms.

Interestingly, the lack of proximity seemed to impact on the types of interactions that GHPs have with the laboratory scientists analysing their patient's data and as well as their confidence in the results that they receive.

Look I've got very close ties with [preferred laboratory] and certainly with exomes we find that the closer the ties that you have with the laboratory and the more you can sit down and chat about the test and what you found, the better the results are... With other relationships, with say [other laboratory] which is in [another country], there's much less communication and we, I guess, trust the results less... But we do use email correspondence to try and identify or get through those communication barriers. Just not quite as good as when you can talk to someone face-to-face.

Participant 22, Clinical Geneticist

Decision-making regarding which laboratories to use

Many of the participants who send their samples to external laboratories indicated that they appreciate the freedom to choose which laboratories they use. They quickly learn which laboratories provide the kind of service they require for different clinical indications

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and use this information to make informed choices for their patients. These decisions are based on a range of factors, including cost, turnaround time, level of interpretation provided, and expertise.

You kind of learn over time to know the pros and cons of a given lab and to interact with their reps... I tend to appreciate the fact that certain labs have expertise in certain types of disorders.

Participant 26, Clinical Geneticist

We definitely are shopping around quite a lot (laughs). And that's because the cost of exome testing is quite variable across the world. Panels are variable across the world as well... If we're thinking more generally and we're not aware of a lab having a particular expertise in that area, or if the lab that does have that expertise does not provide a good service, then we would look around at other options. So, things that we think about are the cost, the turnaround time, we think about how much interpretation we want... And then just being able to communicate with the lab is also important.

Participant 18, Genetic Counselor

Some GHPs were in a position to choose between having their testing performed in-house or externally. In these situations, they were often weighing up between the cost of the test, which was often more expensive when performed in-house, and the quality of the service and level of interpretation provided.

Yeah, so there's a few things that come into the decision about which laboratory to order the testing from. Certainly, when we recruit for the research studies, the laboratory that we use is our local laboratory... But when we order tests outside of that we have to take other things into consideration, including the cost of the test. So, I have ordered a very small number of tests through overseas laboratories because of the difference in cost and what the hospital has been willing to pay.

Researcher: OK. And do they offer a similar kind of a service?

Clinical Geneticist: No. So, they offer an inferior service. But it is cheaper.

Participant 16, Clinical Geneticist

Some GHPs explained that even when the laboratory they were using was not onsite, they could still feel engaged with the process. This was generally when the testing was being

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done on a research basis, but also when they used the same laboratories repeatedly. They discussed how this allowed them to develop valuable relationships with the laboratory scientists based on trust in their expertise.

For whole exome, I typically work with about probably 2 labs... I think having that kind of relationship and trust in a lab is exceedingly helpful. And being able to call them for more information or to offer their insight.

Participant 20, Clinical Geneticist

I like that, you know, I kind of trust that those particular laboratories have the expertise in the condition that we're looking into. So, I guess that kind of makes me, I rely on them in terms of information for the patient. And I know that that's very reassuring for a lot of the patients that I see to let them know that [their sample is] going somewhere where people have expertise in the field and have worked for years and years on particular conditions and genes involved.

Participant 14, Genetic Counselor

Satisfaction with reporting

Regardless of whether they were using in-house or external laboratories, the majority of GHPs valued reports that provided considerable detail. Transparency was key and the GHPs were keen to have all of the evidence that has been used to make a determination about the pathogenicity of the variant laid out clearly in the report.

Some of them provide the background evidence with references to guide their interpretation. Those tend to be the labs we favour because they're comprehensive and you can see their thought process in the interpretation process.

Participant 20, Clinical Geneticist

I like reports to include all of the relevant information in an easily digestible manner so that I don't have to go and look up things on my own, such as population frequencies etc.

Participant 23, Clinical Geneticist

Some of the evidence they felt it was important for laboratories to report included variant frequencies in the general population, conservation between species, protein predictions, possible splicing effects, and the inheritance pattern of the variant in relation to the disease.

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Previous reports of the variant, the clinical presentations of the patients that were identified with the same variant, and citations for references in which the variant had previously been published in the literature were also seen as particularly valuable.

In contrast, two of the genetic counselors highlighted that having detailed, and potentially less 'patient-friendly' reports could make disclosing results to patients quite challenging.

I would like them to be much simpler... I mean obviously all that information is important for the clinicians to know but it is difficult discussing that. It's like a foreign language to them when you're showing a patient, or a family and it's got all this writing about pathogenicity and different types of things... I think sometimes labs can be a bit careless with the wording that they use. So, for example, using words like mental retardation, things like that which I know that they pull up from databases and so on. But things like that can be quite damaging for a family to hear because we don't tend to, obviously, we don't say that in a clinical setting.

Participant 14, Genetic Counselor

Either way, having a clear conclusion or summary which outlines the clinical significance of any variants being reported was flagged as a particularly important component to improve the clarity of the report.

We prefer to keep the reports simpler and to one page because more and more these days the reports are going to other specialists, not necessarily the one that ordered the test, and for them I think it's harder to digest if there's too much information. So, it's important to have that summary, that bottom line, right at the top of the report and then the evidence to guide explanation to the family. Or just to guide management of the variant.

Participant 21, Clinical Geneticist

In terms of the variants that are reported, a small proportion of the participants interviewed were very keen to receive VUS, even in candidate genes. This was because they felt that these had the potential to be the answer to the question for their patient. Yet for these VUS to be valuable, they wanted the report to include detailed evidence so that they can make

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their own judgments about the significance of the variants for the patient, rather than having to go hunting for the information themselves.

I personally appreciate that they tell me the variants of unknown significance of level 3 which could sometimes reveal, or unmask a yet unknown pathogenic mutation... I think "Tell me what it is! Tell me the name, the variant, exactly what it is" because I can also judge it by myself, and then also judge by myself what I want to do with that variant.

Participant 3, Clinical Geneticist

Yet for others, they preferred to receive fewer, or even no VUS and some were of the opinion that a laboratory reporting more VUS was either doing so based on a lack of good interpretation, or concerns regarding liability.

And if you look at, for example, the reports from in the US it's completely different. Because they report everything. But that's because there is not the direct link often between the clinical setting and the lab. They often operate at different [institutions]. So, because of liability, they need to report everything.

Participant 29, Clinical Geneticist

I think the laboratories who report absolutely everything without any assessment... are particularly annoying for referrers. They get a list of 20 or 30 variants without any weighting as to which could be the cause or not. And without an opinion. I think everyone finds that really frustrating and the clinicians who get those types of reports end up thinking, well the laboratory's not doing their job. They want me to make an interpretation of what they should be doing.

Participant 13, Clinical Geneticist

A number of participants felt that close interactions between GHPs and laboratory scientists (either one-on-one or in the MDT) mean that any VUS that are reported are generally highly suspicious and clinically relevant where further investigations, such as segregation testing or functional analysis might help further classify the variant.

And I think what you also get with [preferred laboratory] is quite significant clinical input at MDTs where the phenotype is discussed and whether or not [the variant found] actually fits what would be

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expected for that condition... And often in those meetings what would have been...a variant of uncertain significance, can get upgraded to a [likely pathogenic] because of good clinical phenotype correlation. So, I guess that's where I think I'm seeing this improvement in interpretation or curation with [preferred laboratory] that I don't get with other labs.

Participant 22, Clinical Geneticist

Finally, there was a general sense that building closer collaborations between GHPs and laboratory specialists and providing GHPs with training in GS analysis and variant interpretation, led to better data analysis/interpretation, which result in better reporting and better information to give to patients and their families.

I think this activity is a new thing. It is not a laboratory activity. It is not a clinical activity. It is an amalgamation of those things. And the systems that we have, haven't grown up with that idea. And this is a new thing that, I think, if only we can get people to be cross-trained [in variant interpretation] and work together, the outcomes are going to be much, much better.

Participant 13, Clinical Geneticist

Discussion

To our knowledge, this is the first study to describe the experiences of GHPs interactions with laboratories when requesting diagnostic GS for their patients and when receiving reports following the analysis. Through the interviews, we identified a range of in-house versus external requesting practices, the nature of which appeared to have downstream effects on involvement of the GHPs in the analysis/interpretation process and their perceptions of the quality of what is reported.

The general sense was that a closer interaction between the clinicians and the laboratory scientists, which was more common when the laboratory and genetic service were co-located, increased the involvement of the clinicians in the analysis/interpretation process. This appeared to lead to fewer, but more clinically relevant variants being reported, and greater GHP satisfaction in what is reported. In contrast, when GHPs do not have close

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interactions with the laboratory scientists, which was more common when they are using external laboratories (often commercial companies), they were usually much less involved in the analysis/interpretation process. This seemed to lead to a greater number of variants being reported, many of which are less clinically relevant (or are at least currently lacking evidence to support this). This impact of the relationship between the referring clinician and the laboratory has not been previously described by GHPs in this context. It does, however, support reports by laboratory personnel of the importance of including the referring clinician or other experienced GHPs in the decisions about what to report, either in MDTs or informal discussions (D. F. Vears et al., 2017).

Interestingly, some participants raised the idea of these closer clinician-laboratory scientist interactions leading to greater trust in the results being issued on the report. While we did not explore this in-depth, it would be of interest to investigate the nature of this trust further to establish exactly which aspects of the interaction the GHPs consider signify trustworthiness. Importantly, this close interaction is not necessarily impeded by a lack of close proximity and it was highlighted that repeated contracting of particular external laboratories and use of email could allow for the development of this relationship. This can then facilitate the sharing of more clinical information as required.

We identified an overall preference for laboratories to report a limited number of VUS, predominantly those that are suspected to be related to the clinical phenotype of the patient, yet are lacking sufficient evidence of pathogenicity to be classified as 'pathogenic' or 'likely pathogenic' according to the American College of Genetics and Genomics (ACMG) criteria (Richards et al., 2015). However, there was a small subset of interviewees that showed a preference for also receiving VUS in candidate genes. Current reporting guidelines vary in their recommendations regarding whether VUS should be reported. While those issued by the Canadian College of Medical Geneticists and the European Society of Human Genetics do not specifically address whether VUS should be reported, the ACMG are explicit that they do not support the reporting of VUS (Boycott et al., 2015; Green et al., 2013; van

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El et al., 2013). Whereas Eurogentest leave it to the discretion of individual laboratories (Matthijs et al., 2016), practice guidelines by a Dutch collaboration between their diagnostic centres recommend that “very strong candidate variants that suggest/predict functional impairment and warrant further testing in the family, require reporting” (Weiss et al., 2013). Similarly, a points-to-consider document for laboratories suggests reporting VUS identified in known genes that are related to the clinical question, but also genes not yet associated with the phenotype but where there is evidence that it may be relevant to the phenotype (Vears et al., 2018).

Regardless of their views on the degree to which VUS should be reported, most participants valued detailed reports that lay out the evidence behind the classification of the variant. This is also suggested by a number of reporting guidelines (Matthijs et al., 2016; Richards et al., 2015; Vears et al., 2018; Weiss et al., 2013). GHPs wanted this level of detail in order to allow them to make their own judgments about the relevance of the variant to the phenotype of their patient. This desire for information is likely to reflect the high proportion of our participants that are involved in either the analysis/interpretation of the data or more peripherally, through attendance at MDTs. However, two participants, both genetic counselors, stated a preference for simpler reports, with one commenting on the lack of appropriateness of the terms used on reports for their discussions with patients. Indeed, several of our participants indicated that they talk through the report with their patients and, in some cases, give them a copy. This practice, as well as the fact that non-genetics health professionals are also likely to be working with these reports, supports recommendations for a clear summary paragraph that describes the likely significance of the variants reported in relation to the clinical phenotype of the patient (Vears et al., 2018).

Our participants’ appreciation for what they consider to be ‘good reporting’ (i.e. receiving clinically relevant variants on reports), is reflected in the choices made by the GHPs who are sending some, or all, of their patients’ samples to external laboratories. These participants highlighted that the expertise of the laboratory and quality of the interpretation provided

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was a major factor in their deliberation regarding which laboratory would provide the best service for their patient. However, they also took into account the financial constraints of the health system in which they are operating, which led a number to occasionally compromise on the quality of the reporting in order to accommodate the needs of their patients. Although poor quality reporting may pose less of a risk to patients when testing is ordered by an experienced GHP, it may have a greater impact on patient care if the person ordering the test does not have the genetics expertise to accurately interpret the variants reported.

Although the qualitative approach we have undertaken does not lend itself to generalisation, our findings have important implications for laboratories reporting from GS. First, clearly GHPs consider that integration of clinical expertise into the analysis/interpretation process is critical for ensuring that the variants that are reported are of high clinical significance to patients, which increases their trust in the results reported. We acknowledge that, given the different contexts in which GS are prescribed and performed by laboratories, it may not always be possible for referring clinicians to be involved in the discussions regarding which variants should or should not be reported. Yet, we propose that laboratories that are not affiliated with medical centres should employ GHPs with appropriate clinical experience to assist in the analysis and interpretation process.

Second, as we also identified in previous interviews with laboratory specialists (D. F. Vears et al., 2017), tension remains regarding the reporting of VUS. From our GHPs perspectives, this seems to tie into concerns that some patients may not understand the significance (or lack thereof) of VUS when they are explained at result disclosure (Vears et al. under review). On the one hand, reporting fewer VUS and only those that are considered clinically relevant will make for a less complicated consultation. On the other hand, some GHPs do not want to miss a VUS that could potentially become relevant down the track, particularly if there are no systems in place to routinely reanalyze the data. In such cases, it might be better to

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report the VUS where there is a suspicion that they may become relevant, provided that the report also contains all of the evidence justifying that classification so that GHPs can make their own judgments based on their own clinical experience and knowledge of the patient. Third, as requests for GS from non-genetics clinicians becomes increasingly common, it is crucial that reports contain a clear summary describing the relevance of the variants reported in relation to their likelihood of being the cause of the patient's phenotype.

Finally, our findings suggest the importance of GHPs receiving specialised training in interpreting reports from GS. While this training is being included in current genetic counselling courses, those trained before GS was in use should be provided with opportunities to upskill (either formally or informally) if they are using GS in their practice. This kind of training should also be made available for other specialists without genetics training who may be starting to request GS for their patients.

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