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Reporting practices for variants of uncertain significance from next generation sequencing technologies

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ABSTRACT

The nature of next generation sequencing technologies (NGS) results in the generation of large amounts of data and the identification of numerous variants, for some of which the clinical significance may be difficult to ascertain based on our current knowledge. These Variants of Uncertain Significance (VUS) may be identified in genes in which the function is known or unknown and which may or may not be related to the original rationale for sequencing the patient. Little is known about whether laboratories report VUS to clinicians and current guidelines issued by some of the most notable professional bodies do not provide specific recommendations on this point. To address this, 26 interviews were conducted with 27 laboratory personnel, representing 24 laboratories in Europe (12), Canada (5) and Australasia (7) in order to explore their reporting practices. Participants highlighted that the classification of variants is a real challenge despite the presence of classification guidelines. We identified variation in the reporting practices of VUS across the laboratories within the study. While some laboratories limit their reporting to variants that are pathogenic and thought to be causative of the phenotype, more commonly laboratories report VUS when they are identified in genes related to the clinical question. Some laboratories will also report VUS in candidate genes. VUS that are secondary findings are generally not reported. While it is unclear whether uniformity in reporting is desirable, exploring the perspectives of laboratory personnel undertaking these analyses are critical to ensure the feasibility of any future reporting recommendations.

1. Introduction

Next generation sequencing technologies (NGS), which encompasses targeted gene panels, exome and genome sequencing, are now well-embedded in the clinical setting. NGS is novel in that it allows numerous genes to be analyzed in a single test (Rabbani et al., 2014). For this reason, NGS has played a critical role in the detection of many new disease-causing genes, particularly in the fields of rare diseases and cancer (Guerreiro et al., 2016; Rotunno et al., 2016; Tetzlaff et al., 2016). However, the nature of the technology means that a large amount of data is generated compared to traditional sequencing methods, and the clinical significance of some of these variants might be difficult to ascertain based on our current knowledge (Ream and Mikati, 2014).

These Variants of Uncertain Significance (VUS), also referred to as Class 3 variants by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP), may be unable to be further classified as either (likely) benign or (likely) pathogenic in two main ways (Richards et al., 2015). First, a variant may be classified as a VUS because, despite being identified in a gene known to be related to the clinical question, there is insufficient evidence of pathogenicity. Second, a variant might be identified in a gene of uncertain significance but where the nature of the variant suggests it may be causative of the patient's phenotype (i.e. de novo or truncating variant). In addition, the term "VUS" may also be used to describe a variant lacking evidence of pathogenicity that is identified in a known disease-causing gene that is unrelated to the phenotype of the patient (i.e. an unsolicited or incidental finding).

The guidelines issued by some of the most notable professional bodies do not provide specific recommendations about whether VUS should be reported to clinicians. Instead, they often state that the laboratories should develop, and clearly document, specific

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protocols for the reporting of VUS but leave the decision about whether or not to report these to clinicians to the discretion of each laboratory (Boycott et al., 2015; Matthijs et al., 2016; Rehm et al., 2013; van El et al., 2013). Given the lack of guidance provided, it is difficult to know which variants are being reported to clinicians and whether these practices are consistent between laboratories.

Although one survey conducted with laboratories in the USA asked participating laboratories whether they reported VUS (O'Daniel et al., 2017), reporting practices for VUS have not yet been explored outside the USA. In order to address this knowledge gap, we aimed to assess the reporting practices of laboratories in Europe, Canada and Australasia for variants of uncertain significance to determine which variants are being reported and how decisions about which VUS to report are made.

2. Methods

Qualitative methods were used to explore the reporting practices of laboratories using NGS. Laboratory personnel were recruited using a purposive sampling strategy which sought to identify and recruit individuals who analyze and report the data generated by NGS technologies, including targeted gene panels, clinical exomes, exome and genome sequencing. Potential participants were identified using two strategies. First, internet searches were used to identify laboratories using NGS and laboratory heads were invited to participate via email. Second, snowball sampling was utilized where participants were asked to nominate potential participants from other laboratories they knew were using NGS in the diagnostic context.

Interviews used a semi-structured interview guide and were conducted by one member of the research team (DV). These interviews explored a range of different topics relating to their use of NGS, including the types of technologies and analysis/filtering strategies used in their laboratory, and their reporting practices. Here we report data from components of the interviews discussing their practices relating to variants of uncertain significance. According to the semi-structured interview guide, participants were asked to respond to the following main questions: Which types of results do you routinely report back to clinicians? How do you make decisions about which results to report? What have you found challenging regarding the reporting of findings from NGS?. 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 and 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.

Verbal informed consent was obtained from all participants. 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.

3. Results

3.1. Participant characteristics

Twenty-six interviews were conducted with 27 laboratory personnel - one interview included two participants from the same institution, but from separate groups. This included participants from 24 different laboratories in Europe (12; the Netherlands, France, Germany, Slovenia, Spain, England, Wales), Canada (5) and Australasia (7; Australia, New Zealand). Participants had a mean of 8.1 years (4 weeks–24 years) experience in their current role and a mean of 17.4 years (6–32 years) in the field of genetics. Of the laboratories, 19/24 laboratories operate in the diagnostic context, although several of them also have research components within their laboratory. Although 5/24 laboratories operate purely on a research basis, they were included in the study because they issue reports to referring clinicians. The sample included laboratories that are integrated within a hospital and also some independent laboratories. Twenty of the laboratories use targeted panels (including five who use a mendeliome-based panel), 22 use exome sequencing, (with or without virtual panels), and 4 use genome sequencing (3/4 are research laboratories).

3.2. Challenges associated with variant classification

The participants identified determining which VUS to report as a real challenge for them, describing the tension between reporting and not reporting uncertain variants. This is partly because they found the classification of variants as (likely) benign, (likely) pathogenic, or uncertain as challenging, despite the ACMG guidelines. One participant commented on the subjective nature of the classification of variants, even when using classification guidelines, and how this could easily result in differences in classification of variants between individuals.

> It still is a challenge, every time you write a letter, especially for the exome sequencing. Because you often do have the feeling like, this is probably not something. But a feeling alone is not enough. […] You do classify those variants based on certain aspects and I find it's sometimes difficult when you have a feeling that this probably, it's nothing. But you have to put a 'class 3' on it, because you don't have enough proof that it is basically not a disease causing mutation.
>
> Participant 20

> One of those things that really worries me, it's like that it will depend so on the people. People report different things. For example, my colleagues and I will not always agree on the thing we have to report. But also it could depend on your mood and for me it's always really stressful because when you have time, […] you will spend more time on one specific variant to follow it and really search if it could be or not involved in the disease. And if you have maybe less time […] you will discard it maybe. […] And so for me, what is challenging is to deal with this need to be like, quite objective but also the need to be subjective because it's your experience of molecular biology that can really help you to interpret a variant.
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> Participant 25

3.3. Reporting practices for variants of uncertain significance

The interviews with laboratory personnel indicated that some laboratories, including many of those that operate solely in a research context, do not routinely report VUS to referring clinicians.

> That's obviously a point of ongoing discussion, but I was always pretty keen on reporting less rather than more. Certainly, you know, I've seen reports where there's a whole page of, you know, class 3 variants on the back of the report. I've always been very anti-that. So, we routinely report class 4s and class 5s. Very, very rarely will I actually ever include a class 3 variant on a report.
>
> Participant 13

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Those who would not report VUS discussed their concerns that health professionals would over-interpret the significance of VUS if they were reported, with some participants citing specific examples of when this had occurred. This could lead to the health professionals overemphasizing the likely importance of the finding if they disclose the presence of the VUS to the patient. They also raised issues such as the difficulty of "unlabeling" patients if they are wrongly "diagnosed" because a VUS is misconstrued as a result, concern about the difficulties in explaining VUS to patients who may not understand what it means and may be worried or scared about the "result", and that reporting VUS will lead to unnecessary follow up for patients, including any additional costs these might incur.

> And this physician […] told the family it was probably the cause of the disease. And she wanted to do prenatal testing in this family and we said 'no, we cannot do that. It's a class 3 variant and we do not want to do prenatal testing on that'. So there are the examples, especially for class 3. Sometimes physicians do explain it different than we wanted them to say. And then sometimes I think OK, maybe we should not report the class three then and just keep it in our database and then tell them if we could upgrade it to a class 4 or something.
>
> Participant 5

> For the patient, it's hard enough to understand the genetics, for example, that a variant is really disease causing and that it's de novo, dominant, or recessive or whatever. I mean, explaining this takes lots of time […] But to come around with, I don't know, 50 different variants and try to explain whether this is clear or unclear or not clear, I think that it's too much for the patient and maybe the patient will be scared about all these results and all this different information. Information which he cannot judge himself.
>
> Participant 7

However, many of the laboratories will report VUS if they are thought to be relevant to the clinical question, although they are lacking sufficient evidence to classify them as pathogenic. Obviously, the laboratories that only perform testing using gene panels, or limit their analysis of exomes to genes that are relevant to the clinical question using virtual panels, will only find VUS of this type.

> We do not report the variants of unknown significance in the reports unless they are clinically relevant with a phenotype, but we lack functional data or biological data to demonstrate its pathogenicity, or we lack biochemical testing to assess the, the pathogenicity of this variant.
>
> Participant 18

Of those who stated that they would report VUS, they expressed sentiments such as that they would prefer to report them rather than miss a potentially causative VUS and argue that the relevance of variants might change as knowledge in the field increases. Some interviewees also felt that reporting VUS to clinicians may allow further classification of the variant. One participant discussed that, in their experience, clinicians like to be informed and that reporting the variants to them is a sign of respect for their expertise.

> It's not so important when you've got a very clear mutation, something that's already known, something which is well established in the literature. But if you don't have that, then I think people like to know […] why we've called it a variant of unknown significance. Then if something changes, you know, if […] in the next 5 years someone publishes another case […] or someone does segregation studies in the family, then you can add that in as independent information and the clinician themselves can then decide whether that adds sufficient extra information that they could then call that pathogenic. It just sets out our reasoning in a very, very clear fashion. I think it's helpful. Clinicians love it. And it treats them with respect I think.
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> Participant 15

Very few laboratories indicated that they report VUS in candidate genes when they are not certain that they are relevant to the phenotype. For those that may report these types of VUS, they may decide to do so for one of three reasons. This may be because no pathogenic variants have been identified, there is some evidence of pathogenicity or the variant looks functionally suspicious, such as a de novo or truncating mutation, or they may have identified two VUS in the same gene in a patient and the inheritance is consistent with an autosomal recessive condition.

Laboratories would generally not report VUS in genes that are disease-causing but that are unrelated to the clinical question (i.e. a VUS which is also an unsolicited or incidental finding) and a number of participants expressed discomfort around doing so. However, a small number of participants explained that if these types of VUS were identified, they would be discussed within their team meetings.

> There is a discussion to be had whether an incidental variant of unknown significance should be reported. […] At this stage it's a case-by-case discussion. Personally, I think if you don't know what the variant means, and if it's definitely not linked to the phenotype but might cause something completely different, it would be irresponsible to report it but […] that's a decision that would be made in consultations with a wider group of experts.
>
> Participant 11

3.4. Differentiating VUS from causative variants in the reports

Some participants indicated that if they are reporting VUS they do so in a table or a separate page of the report in order to avoid confusion for the clinicians and differentiate the VUS from actual results.

> So we decided in the working group […] in the first page of the report that we will give back to the clinician only class 4 or class 5 mutations. So pathogenic or probably pathogenic mutations […] So it was like a really conscious decision to say that if we have to talk about a variant of unknown significance we can mention in the first page that we found variants of unknown significance but we don't have to give the information at the same place where we put variants that we think they are probably or certainly pathogenic. Just to be sure that there won't be a misinterpretation or a novel interpretation by the clinician.
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> Participant 25

When VUS are reported, laboratories put varying degrees of information about the variants in the report. Some laboratories provide a lot of information about the VUS, including their argumentation about why the variant has been classified within this category. One laboratory that we studied described the additional categories they use within their laboratory to subdivide VUS into

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three subcategories in order to provide more information about the strength of the evidence relating to the VUS.

> Where we report a class 3, we will use a sub-descriptor class 3A, 3B and 3C, where class 3A is a variant of uncertain clinical significance with predominantly pathogenic evidence, and a class 3C is the same but with predominantly benign evidence.
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> Participant 15

In contrast, other laboratories prefer to make their reports clear but concise and may only include one sentence where they mention that they have found a VUS, report the name of the gene in which the variant was identified, and then leave it to the clinician to ask for additional details if they wish to know more.

3.5. Decision-making regarding which variants to report

Many of the participants indicated that decisions about reporting VUS were rarely made solely by the laboratory specialist performing the analysis. Instead, decisions would either be made in informal discussions with other colleagues, or more formal meetings that often involve multidisciplinary committees.

> So every four weeks we present the variants […] in a meeting which we call the 'exome meeting'. And there < we also discuss > things like the report […] and things like that we are not reporting all unclassified variants and only the ones which there is more proof in the literature or where there are other patients in the database with variant in these genes. We report those and the other ones we just put in the disclaimer […] We discuss that together so these decisions are made, yeah, together.
>
> Participant 10

Some participants may discuss VUS with the referring clinician before issuing a formal report in order to obtain more information about the patient's phenotype or ask for additional samples from family members to determine the segregation pattern of the variant.

> So there is a fair bit of dialogue actually with the clinicians, even before we report if we're not sure. […] You know, it might be fairly frequent but it's an autosomal recessive and we have another mutation in the same gene and if we do some family studies and we see that one and the other, it may actually push it over the line. We will correspond with the clinicians and say look, this is what we found. Do you want to go back to the patient and just discuss this with them before we report it?
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> Participant 14

4. Discussion

Our interviews showed variation in the reporting practices of VUS across the laboratories included within the study. While some laboratories limit their reporting to variants that are thought to be causative of the phenotype, it was more common for the laboratories in our study to report VUS when they are in genes related to the clinical question. This corresponds with the results of the US-based study where 19/20 of the laboratories reported VUS that were thought to be related to the symptoms of the condition for which testing was originally requested (O'Daniel et al., 2017). However, our interviews showed that some laboratories we included are also reporting variants in candidate genes, which has not been reported previously.

The laboratories in our study generally did not report VUS in disease-causing genes unrelated to the clinical question, which corresponds with the results of the US-based study were none of the diagnostic laboratory respondents reported VUS for secondary findings (O'Daniel et al., 2017). This is also in line with the ACMG reporting guidelines for secondary findings that recommend reporting only class 4 and class 5 variants in their list of 59 disease-causing genes (Kalia et al., 2016). This seems appropriate in light of the calls by professional bodies for targeted sequencing approaches in order to reduce the number of variants identified, particularly in genes unrelated to the original rationale for testing (Boycott et al., 2015; Matthijs et al., 2016; van El et al., 2013).

Many of the concerns that were raised by our participants regarding the reporting of VUS related to the potential for a VUS to be treated as an actual result, rather than an uncertain variant. They held concerns that these VUS would be over-interpreted by the referring clinicians that could lead to unnecessary follow up for patients, and pose an additional burden on the health care system. Indeed, some participants mentioned cases where clinicians had clearly over interpreted a class 3 variant and had conveyed this misinterpretation to the patient as the cause of the disease. These concerns meant that some of the participants felt they were performing a balancing act of sorts between the desire to be cautious in their reporting but also wanting to ensure that a potentially causative variant is not “missed”.

Some laboratories described how they had developed reporting strategies in order to reduce the risk of over-interpretation of VUS, such as adding a separate table, an additional page, or outlining the evidence associated with each variant in detail on the report. While some thought the referring clinicians to whom they were issuing reports had a good understanding of NGS and appreciation of the limitations of the testing, a large proportion of the participants had doubts about this. This sentiment was more commonly expressed when referring clinicians were disease-based specialists, rather than clinical geneticists, and were therefore often lacking the training and expertise to be able to sift through the lines of evidence provided for a given variant. Our participants called for more education for clinicians in NGS in order for them to have a better understanding of the results being issued and several of the experienced laboratories organize training sessions for clinicians for precisely this reason.

The variation between laboratories leads us to consider whether it is desirable, let alone feasible, for uniformity in practices across laboratories with regards to the reporting of VUS. While clearly there are aspects of laboratory practices for which standard operating procedures are critical, such as quality control aspects, are reporting practices for VUS an aspect where laboratories should be able to exercise professional autonomy, as per recommendations by professional bodies (Boycott et al., 2015; Matthijs et al., 2016; Rehm et al., 2013; van El et al., 2013)? To answer this question we must consider what is at stake if laboratories are allowed discretionary rights in the reporting of VUS.

The main risk in this situation is that a variant for which there is insufficient evidence to be classified as either (likely) benign or (likely) pathogenic at the time of the analysis will be “lost” in the system. As our knowledge in this field increases, we assume that many of the variants currently classified as VUS will become more definitively classifiable and that, for some patients, this will be the “answer” for their genetic disorder. Interviews with health specialists and laboratory personnel in the UK identified that, although there was lack of clarity regarding who currently initiates this kind of reanalysis, overall the preferred model was for this request to come from the clinician, although some felt patients should at least

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partially share this responsibility (Carrieri et al., 2017). Yet, if laboratories are not in the habit of regularly reassessing VUS, and the VUS have not been reported to clinicians, then it makes it less likely that clinicians, or patients, will think to request for their data to be reanalyzed in light of evolving knowledge. While the practical feasibility of reanalysis of VUS and re-contact of patients will be dependent on the infrastructure and resources of each individual service (Otten et al., 2015), reporting VUS to clinicians may help facilitate this process as the burden is shifted from the laboratory to the clinician caring for the individual patient.

From an ethical perspective, it is unclear whether laboratories should be reporting VUS in genes that are related to the original rationale for testing. One could argue that, given that the uncertainty of the status of the variant, a VUS would not be classified as health-related *information per se*. However, if reporting were to increase the likelihood of a VUS being reassessed which led to the identification of a causative variant in a previously undiagnosable individual, then perhaps in the clinical setting, where the goal is promotion of overall health and wellbeing, one could argue that laboratories should report VUS to clinicians. Of course, this likelihood, and therefore the clinical utility of a VUS, cannot be predetermined.

Of note is that even if policies for the reporting of VUS become standardized, the classification of the variants is an aspect that even experienced laboratory personnel are still finding challenging. This was highlighted both by the laboratory that have added subcategories to their class 3 classification, and our participant who discussed their struggle with the subjective nature of variant classification, despite the presence of detailed recommendations for this (Richards et al., 2015). Although clearly standardization of classification systems is important, it is easy for non-laboratory clinicians to forget that the person who carries out the classification is drawing on their experience and expertise at every step and that the decisions made by these “invisible technicians” are the difference between a correct or incorrect diagnosis (Shapin, 1989). While this subjectivity may be the difference between these two, it emphasizes the necessity for decisions about which variants should be reported to be made with the assistance of others. In line with this, our participants highlighted the importance of case discussion about VUS, as well as pathogenic/likely pathogenic variants and unsolicited findings, and the value in being able to draw on the expertise of other colleagues and clinicians, both those referring patients and within multidisciplinary committees.

Our study did not include laboratories from all countries within Europe, largely because it was difficult to determine which laboratories were performing NGS and many do not currently offer NGS in the diagnostic setting. We acknowledge that laboratory practices are likely to be in a constant state of flux and that these results are therefore only representative of the time the interviews were conducted. In line with our qualitative methodology our findings are not intended to be generalizable to the population. We also did not attempt to compare practices across continents/countries. Instead, we have attempted to understand the scope of practice in the field and have identified that practices for the reporting of VUS vary between the laboratories we included. The jury is still out as to whether we should be aiming for uniformity in the reporting of VUS. This determination would require further engagement and detailed discussions with a range of stakeholders, including clinicians, ethicists and lawyers, to explore what is ethically and legally appropriate. However, the responses from various participants suggest they would favour a policy for laboratories to report VUS, provided they are in genes which are either known to be related to the clinical question, or in candidate genes where there is some evidence to suspect that they are the cause of the phenotype in the patient. In addition, they suggest that VUS be reported in a way to distinguish them from validated results, such as in a table or on a separate page of the report. If uniformity in reporting was deemed desirable, explorations of the perspectives of laboratory personnel undertaking these analyses, such as ours, are critical to ensure that any reporting recommendations are feasible.

Conflict of interest

The authors have no conflict of interest to declare.

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