Full title: *What are the ethical concerns regarding reporting and disclosing variants of uncertain significance identified via genetic or genomic testing? A systematic review of reasons.*

Short title: *Ethical considerations regarding disclosure of uncertain genetic variants.*

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Abstract

Genetic tests frequently generate variants of uncertain significance (VUS), where a genetic change is found but it is unclear whether it is causing a patient's symptoms, or whether it is just benign genetic variation. With increasing use of broad genetic testing (such as exome or genome sequencing), VUS are being found more often. However, decisions about whether to record VUS on the formal laboratory reports that document the outcome of genetic testing, and whether to disclose VUS to patients, can be controversial. This systematic review of reasons examined the ethical arguments surrounding the decisions whether or not to report and disclose VUS. It involved a systematic search of MEDLINE, EMBASE, CINAHL, PsycINFO, SCOPUS and PhilPapers to identify relevant literature on this topic.

Out of 1434 publications, 26 were selected for data extraction. 92% of the included publications had been published in the last decade. The publications discussed reporting and disclosure of VUS in a variety of contexts, with VUS identified in a prenatal setting representing the largest group (46%), followed by VUS identified via broad genomic testing (23%), and VUS identified in the context of research studies (12%). Ethical arguments identified from analysis of the publications pertained to the relationship between VUS disclosure and respect for patient autonomy, whether VUS can be seen to have a status as medical information, the risk of personal and societal harm arising from VUS disclosure or non-disclosure, and the handling of uncertainty and the need for resolution. Whilst finding a yes/no answer to the normative question of whether to report and disclose VUS is beyond the scope of a systematic review of reasons, these findings demonstrate the challenge of reaching a decision on VUS reporting and disclosure, and raise aspects to consider when faced with this decision on an individual patient basis.

Author's summary

Sometimes when we find a genetic spelling change, we are unsure whether the change is causing health problems, or whether it is just natural genetic variation and not causing any health problems at all. These genetic spelling changes are called 'variants of uncertain significance' (VUS). When VUS are found, it can be difficult to decide whether to note them in medical records and communicate them to patients or not. My project looked at the ethical aspects of these decisions. I searched six academic databases looking for articles that discussed this issue and found 26 relevant articles. Most were written in the last decade, and lots focused on VUS found from genetic tests during pregnancy. The ethical issues discussed in the articles included whether communicating VUS helped patients to take

control of their own lives and medical decisions, and whether it was reasonable to see VUS as medical information or not. Other issues included whether patients could be harmed by being told about VUS, and how to handle uncertainty. My research showed that decisions about whether to communicate VUS or not are complex, and raised various issues that need to be considered when making these decisions.

Introduction

Broad genetic testing has now become part of mainstream clinical practice, but our technical ability in generating sequence data has far outstripped our ability to interpret it. This means that many broad genetic tests find variants of uncertain significance (VUS), where a genetic change is found that may or may not be responsible for a patient's problems. Decisions over whether or not to disclose VUS from genetic testing can be controversial[1]. The current consensus recommendation of the American College of Medical Genetics and Genomics is that VUS should not be used in clinical decision making (for example VUS should not influence decisions regarding screening or preventative treatments, and should not be used to inform the care of a patient's wider family)[2]. This view is also broadly shared by the Association for Clinical Genetic Science in the UK, though they recognise some limited situations where using a VUS as evidence supporting a likely clinical diagnosis may help the patient in accessing appropriate support[3].

One concern has been the risk of variant misinterpretation and the harm that this could cause to patients and families. For example, Ackerman *et al*. described a family where a rare variant in *KCNQ1* was found in the brother of a teenage boy who died suddenly. The *KCNQ1* variant was assessed as being causative of long QT syndrome. The boy's sudden death was attributed to this (without any genetic testing being undertaken on samples from him), and the living brother had an implantable cardioverter defibrillator inserted based on his genetic test result. Via cascade genetic testing, over 24 relatives were diagnosed as having long QT syndrome, despite having normal QT intervals on ECG. Over time, the family challenged the diagnosis, and subsequent testing showed that the deceased child did not have the *KCNQ1* variant that was found in the living brother, and had changes on postmortem that were inconsistent with a diagnosis of long QT syndrome. Postmortem exome testing then found that the child who died had a clearly disease-causing variant in *DES* (a gene linked to cardiomyopathy) that would account for his sudden cardiac death, and that this variant had occurred for the first time in him rather than having been inherited through the family[4].

Misinterpretation of a VUS as pathogenic is also the focus of an ongoing lawsuit in Oregon, where a 36-year-old woman had a bilateral mastectomy and hysterectomy as she believed she was at significantly increased risk of cancer after being found to have an *MLH1* variant. Pathogenic *MLH1* variants are associated with Lynch syndrome, a hereditary cancer syndrome conferring an increased risk of colorectal, endometrial, and various other cancers (risk of breast cancer is not clearly increased so prophylactic mastectomy would not generally be indicated for women with Lynch syndrome in any case[5]). The *MLH1* variant identified in the plaintiff was of uncertain significance and not clearly pathogenic. She has recently initiated a $1.8 million medical malpractice lawsuit against the healthcare professionals who counselled her regarding her genetic test result, claiming that had she been told that the significance of her *MLH1* variant was uncertain, she would not have chosen to have major surgery in an attempt to reduce her cancer risk[6]. These cases illustrate the potential morbidity in misinterpreting a potentially benign variant as pathogenic, in exposing patients to invasive and inappropriate procedures such as major surgery if they are erroneously thought to have a genetic disease. Inappropriate management of a VUS as if it were pathogenic can also be dangerous in providing false reassurance, as people who do not have the variant may miss out on clinical screening and potential treatment, despite still being at risk of developing disease.

Many VUS will turn out to be benign[3]. However, over time some will emerge as pathogenic. This means that non-disclosure of VUS can also be seen as a risk, especially in cases where with collaborative work with other laboratories or researchers, or by tracking the VUS through a family to see whether it segregates with disease, it may be possible to reclassify a variant as pathogenic[7]. Failing to do this may result in missing a genetic diagnosis, preventing informed clinical management for patients and families. Another concern is that patients may not seek updated genetic advice in the future if they do not know that a VUS has been found from their genetic test. Currently we do not have clear protocols in place to re-contact people when new genetic information comes to light that may be relevant for them[8]. Therefore, if a patient is not informed of a VUS identified via genetic testing, it is not clear how and whether they would be updated if the variant were later to be reclassified as clearly pathogenic or clearly benign. In contrast, if they know that they have a VUS they may be more likely to seek updated genetic advice at relevant points in their life.

Currently, there is considerable focus on the technical aspects of whether to report VUS, for example

increasingly sophisticated bioinformatic programs to assess the likely pathogenicity of particular amino acid changes, and enlarging databases of natural genetic variation with curated databases of pathogenic variants[9]. There has also been an emergence of multidisciplinary meetings where clinical scientists, clinical geneticists, and other healthcare professionals meet to discuss whether or not to report VUS identified via genetic testing[10]. However, whilst the technical aspects of whether or not to report variants are analysed in great depth, based on personal clinical experience there is often little formal assessment of the ethical issues surrounding whether or not to report a particular variant.

Decision-making regarding whether to report or disclose VUS is a key aspect of modern genetic practice, and as genetic testing becomes mainstream, non-specialist healthcare professionals will also need increasing understanding in this area[11]. The current reporting guidelines for UK genetic laboratories recommend that VUS should only be reported to clinicians with experience in this area, or that when reported to non-specialists, extreme caution should be taken and it would be appropriate to suggest that they seek advice from a clinical geneticist[12]. There is also a school of thought that the potential harms of inappropriate interpretation of VUS are so great that laboratories should only report pathogenic variants, and this stance is often adopted in the UK when undertaking genetic testing in the context of an ongoing pregnancy[13,14].

Clearly it is important to make some assessment of the ethical aspects of decisions regarding whether to report and disclose VUS. Systematic reviews of reasons are emerging as a recognised way to consider ethical questions. Historically, standards for decision making relating to ethical issues have been determined by eminence-based input and expert discussion, rather than by systematic analysis of relevant normative information[15]. The aim of systematic reviews of reasons is to answer an empirical question of which arguments have been cited in the literature when reflecting on a specific ethical topic, rather than to normatively answer an ethical or moral question[16]. The purpose of a systematic approach is to collate a comprehensive set of reasons for or against a particular course of action, whilst also aiming to minimise bias when summarising ethical arguments collected from academic literature[17].

This review aimed to delineate the ethical arguments presented in existing academic literature regarding whether or not to report and disclose VUS identified via genetic testing. This involved systematic searching of MEDLINE, EMBASE, CINAHL, PsycINFO, SCOPUS and PhilPapers to extract relevant literature on whether to report and disclose VUS from genetic testing, followed by extraction of ethical arguments for and against each course of action. It identifies a number of themes raised in the ethical literature on this topic, including the potential impact of VUS disclosure on patient autonomy, whether VUS can be seen to have a status as medical information, the risk of personal and societal harm arising from VUS disclosure or non-disclosure, and the handling of uncertainty and the need for resolution.

Materials and Methods

The methodology for this systematic review was developed with reference to the PRISMA checklist[18] and the ENTREQ statement[19]. The project and methodology are registered on the Open Science Framework (https://osf.io) with Digital Object Identifier: osf.io/3w98m.

Search strategy

Scoping searches were undertaken using the TRIP database and PubMed to facilitate search syntax development by review of author keywords and MeSH terms of relevant publications. In initial scoping searches, 'genetics' was not mentioned in the search terms in order to maximise sensitivity. However, it was later included in the main searches as without it the search results were insufficiently specific.

Six bibliographic databases (MEDLINE, CINAHL, Scopus, PsycINFO, PhilPapers, EMBASE) were searched for relevant literature from their inception until November 2017. Several databases were selected in order to encompass a broader range of literature and to exploit the different strengths of each database in finding relevant literature. MEDLINE and EMBASE were selected to maximise the chance of extracting relevant literature from medical sciences publications, and PsycINFO was selected as some discussion of VUS in the literature may be in the context of psychological impact and this database would be well placed to find these. CINAHL was used as this gives rich information from nursing and allied health professions journals, and much of the literature on VUS may be published in genetic counselling journals which would be likely to be represented in this database. Scopus was selected as it contains very broad-ranging literature and PhilPapers was selected to try to minimise the chance of missing relevant publications on VUS that may be published in primarily philosophical journals rather than medical science journals.

Table 1 shows the search terms used for each database. Search syntax was developed with guidance from a research engagement librarian. The results of each search were downloaded to Endnote Web (available via www.myendnoteweb.com), and duplicates were removed.

Table 1: Search syntax

Database	Syntax
MEDLINE (via Ovid)	1. ethics/ or bioethical issues/ or exp bioethics/ or exp ethical analysis/ or exp "ethical review"/ or ethical theory/ or exp ethics, clinical/ or exp principle-based ethics/ 2. ethic*.mp. 3. bioethic*.mp. 4. "ethical issue".mp. 5. "ethical guideline".mp. 6. normative.mp. 7. moral.mp. 8. "ethical issues".mp. 9. "ethical guidelines".mp. 10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 11. uncertainty/ 12. variant of uncertain significan*.mp. 13. variant of unknown significan*.mp. 14. VUS.mp. 15. VOUS.mp. 16. unclassified variant.mp. 17. unknown variant.mp. 18. ambiguous variant.mp. 19. (varia* adj3 uncertain).mp. 20. (varia* adj3 unknown).mp. 21. (varia* adj3 significan*).mp. 22. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 23. 10 and 22 24. genetic*.mp. 25. genetics/ or exp genetics, medical/ 26. genom*.mp

	27. 24 or 25 or 26 28. 23 and 27
CINAHL (via EBSCOhost)	1. DE "Professional Ethics" OR DE "Bioethics" OR DE "Morality" OR DE "Ethics" 2. (ethic* OR bioethic* OR normative OR moral) OR ("ethical issue" OR "ethical issues") OR ("ethical guideline" OR "ethical guidelines") 3. S1 OR S2 4. DE "Uncertainty" 5. variant of uncertain significan* OR variant of unknown significan* OR (VUS OR VOUS OR unclassified variant OR unknown variant OR ambiguous variant) 6. varia* N3 uncertain OR varia* N3 unknown OR varia* N3 significan* 7. S4 OR S5 OR S6 8. S3 AND S7 9. DE "Genetics" OR DE "Genetic Counseling" 10. genetic* OR genom* 11. S9 OR S10 12. S8 AND S11
Scopus	(TITLE-ABS-KEY (ethic* OR bioethic* OR normative OR moral OR “ethical issue” OR “ethical guideline”)) AND ((varia* W/3 uncertain OR varia* W/3 unknown OR varia* W/3 significan* OR VUS OR VOUS)) AND (genetic* OR genom*)
PhilPapers	Search mode: fuzzy filter (basic) Entry contains at least one of these words: (variant NEAR:3 significan*) AND Entry contains at least one of these words: uncertain unclear unknown
PsycINFO (via EBSCOhost)	1. DE "Professional Ethics" OR DE "Bioethics" OR DE "Morality" OR DE "Ethics" 2. (ethic* OR bioethic* OR normative OR moral) OR ("ethical issue" OR "ethical issues") OR ("ethical guideline" OR "ethical guidelines") 3. S1 OR S2 4. DE "Uncertainty" 5. variant of uncertain significan* OR variant of unknown significan* OR (VUS OR VOUS OR unclassified variant OR unknown variant OR ambiguous variant) 6. varia* N3 uncertain OR varia* N3 unknown OR varia* N3 significan* 7. S4 OR S5 OR S6 8. S3 AND S7 9. DE "Genetics" OR DE "Genetic Counseling" 10. genetic* OR genom* 11. S9 OR S10 12. S8 AND S11
EMBASE (via Ovid)	1. ethics/ or exp bioethics/ or ethical theory/ or exp medical ethics/ 2. ethic*.mp. 3. bioethic*.mp. 4. "ethical issue".mp. 5. "ethical guideline".mp. 6. normative.mp. 7. moral.mp. 8. "ethical issues".mp. 9. "ethical guidelines".mp. 10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 11. exp uncertainty/ 12. variant of uncertain significan*.mp. 13. variant of unknown significan*.mp. 14. VUS.mp. 15. VOUS.mp. 16. unclassified variant.mp. 17. unknown variant.mp. 18. ambiguous variant.mp. 19. (varia* adj3 uncertain).mp. 20. (varia* adj3 unknown).mp.

	21.	(varia* adj3 significan*).mp.
	22.	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
	23.	10 and 22
	24.	genetic*.mp.
	25.	exp medical genetics/ or genetics/
	26.	genom*.mp
	27.	24 or 25 or 26
	28.	23 and 27

The database searches were supplemented by manual searching of reference lists of included publications, and manual screening of forward citation searches for included publications using Web of Science (http://webofknowledge.com/) and Scopus (https://www.scopus.com/). Publications identified as potentially relevant were screened as described below.

Screening and eligibility

Search results were assessed by manual review. Rayyan[20], a freely available app designed to expedite screening of abstracts and titles, was used to facilitate the screening process (https://rayyan.qcri.org/). Publication selection involved initial review of titles and abstracts, rejecting those that clearly did not meet the inclusion criteria. The full text of the remaining potentially relevant publications was then read, and publications that met the eligibility criteria proceeded for data extraction.

Publications were included if they were:

1. Written in English (as this research did not have a budget for translation of publications in other languages).
2. Explicitly reporting on ethical aspects relating to reporting or disclosure of VUS. Criteria to assess this were used as per Mertz *et al*. who developed a detailed breakdown of this as part of a systematic review of ethics literature reviews (e.g. publication had to pose an ethical question, determine ethical problems/challenges, address ethical decision making, etc. It was not sufficient for a publication just to state that there were some ethical issues)[15]. 'Reporting of VUS' related to decisions whether or not to record VUS on the formal report documenting the outcome of genetic or genomic testing. 'Disclosure' encompassed reporting decisions but also included decisions whether or not to communicate VUS to patients.

Publications were excluded if:

1. They did not meet inclusion criteria.

Data extraction and analysis

For publications eligible for inclusion, the first author, date of publication, country of corresponding author, publication type and research focus were recorded. Beginning with the abstract and proceeding to the full text, ethical reflections or arguments presented in included publications were categorised into: arguments in favour of reporting or disclosing VUS; arguments against reporting or disclosing VUS; arguments that caution about reporting or disclosing VUS; arguments relating to disclosure of VUS. Appendix Supplementary Figure 1 shows the data extraction proforma used. The collated arguments from the included publications were then analysed to look for common themes.

Each included publication was assigned a unique number, then a random number generator was used to select 10% of the publications for independent data extraction and analysis for themes by a second researcher (my primary supervisor). Any discrepancies between data extracted for this subset of publications was resolved by discussion, prior to wider discussion between the two researchers of the common themes identified from the collated arguments extracted from all included papers.

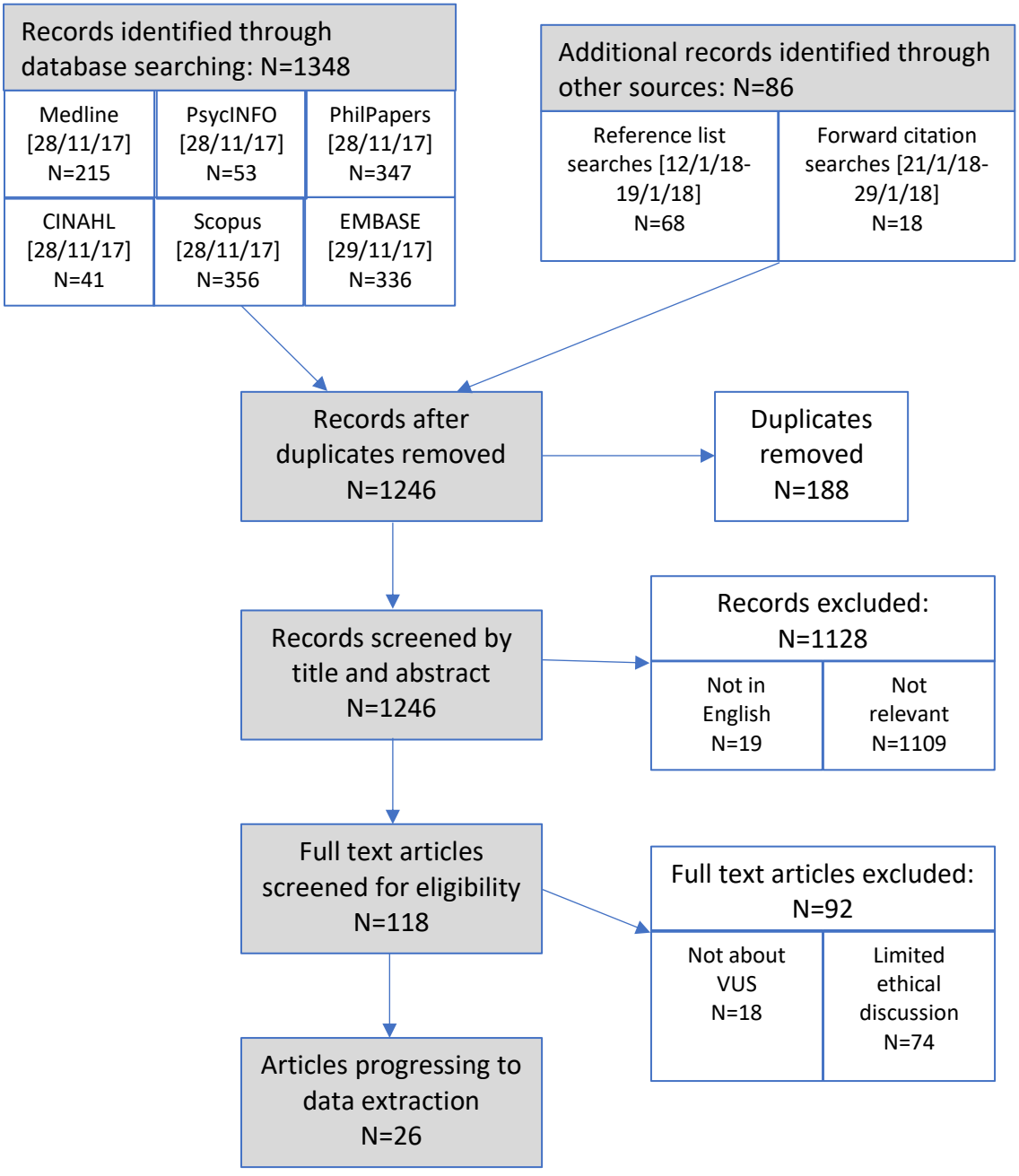
As per common practice in systematic reviews of reasons, no quality assessment was made of the included publications[21]. The rationale for this is that publications where methodology and analysis methods are not explicit may still make an important contribution to the breadth of systematic reviews of reasons. The number of times that specific reasons were cited in the literature was not recorded, as the aim of this review was to delineate the range of arguments given in the literature, in keeping with standard practice in qualitative research[22]. The frequency with which a particular argument is mentioned is not considered to be a useful marker of its ethical importance. However, the proportion of publications that broadly discussed various aspects of each of the common themes was noted.

Results

Screening and filtering process

From the initially identified 1434 references, 26 publications were selected for data extraction as shown in Figure 1. The subsequent results represent the selected 26 publications (please see Appendix Supplementary Table 1 for list).

Figure 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart

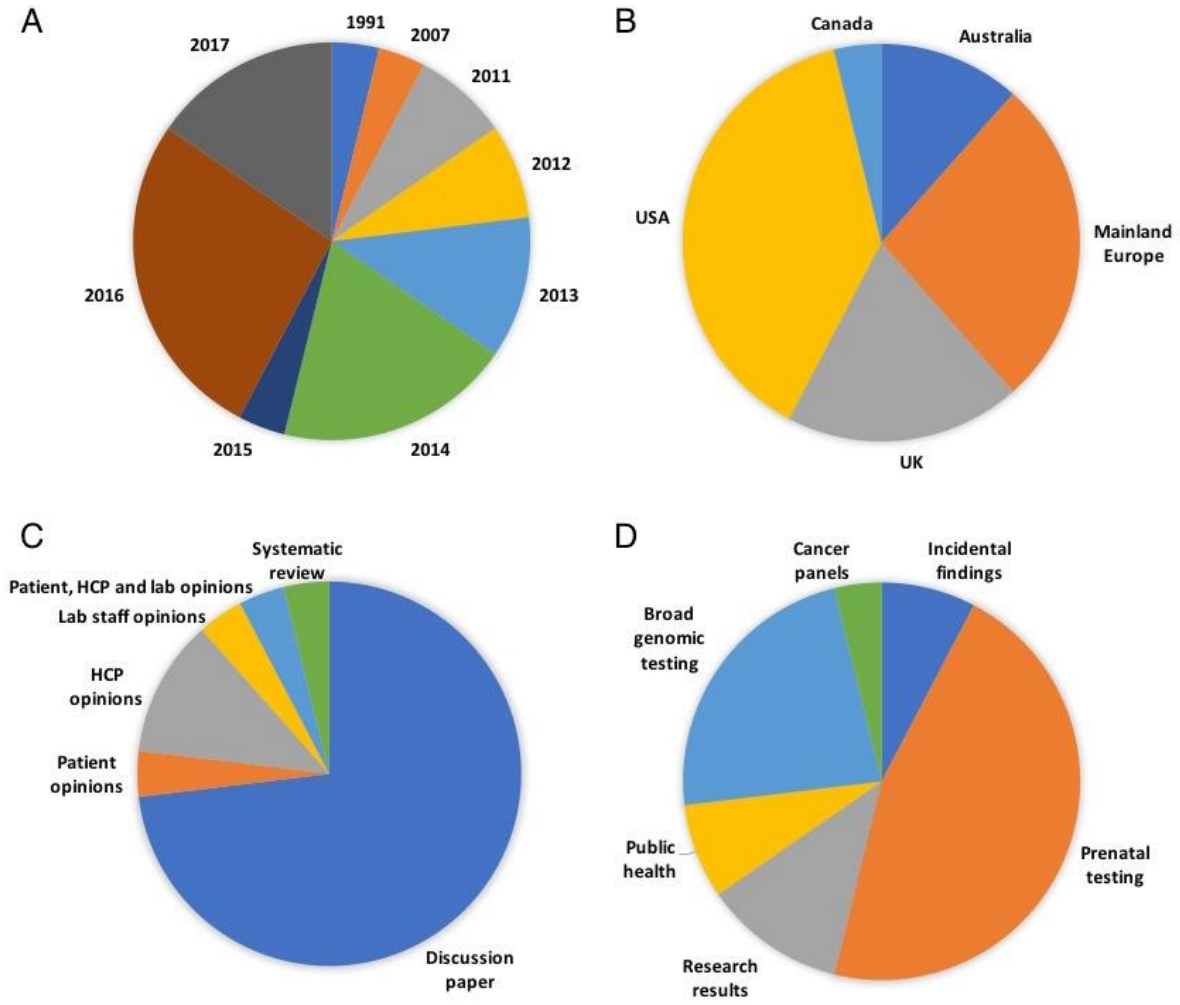


Publication characteristics

92% of the 26 included publications were published in the last decade (N=24). Nineteen were discussion papers, six were qualitative studies collating opinions from various stakeholders, and one was a systematic review. Ten publications were written by authors from the USA, seven from mainland Europe, five from the UK, three from Australia, and one from Canada. Twelve publications focused on the issue of VUS in the context of prenatal testing, six publications discussed VUS in the

context of broad genomic testing, and three focused on VUS identified via research. Two publications discussed VUS in the context of public health screening, and two discussed incidental findings of unknown significance. One publication discussed VUS identified via cancer gene panels. Figure 2 represents the characteristics of the included publications.

Figure 2: Characteristics of included publications
(A) Publication dates; (B) Country of corresponding author; (C) Type of publication
(D) Context in which publication discusses VUS



Analysis of themes

The relationship between autonomy and disclosure

The potential impact on patient autonomy was cited by fifteen publications as a consideration in whether or not to disclose VUS[23-37]. Eight publications discussed that non-disclosure of VUS could be seen as paternalistic[14,24-27,29,31,38]. Three publications considered patient autonomy to be an overriding consideration in favour of disclosure[24,27,36] (for one publication this was in the context of a head-to-head discussion article[24]):

> '*In this era, a paternalistic approach to medical care is no longer considered acceptable, and the ethical principle of autonomy therefore mandates disclosure of the information*'[24]

For one of these three publications, they explained that '*the principle of autonomy embodies respect for the patient's right to choose or to refuse treatment*'[24]; the other two publications did not provide a definition for autonomy.

Seven publications discussed that different definitions of autonomy would lead to different conclusions regarding VUS disclosure[23,25,26,28-30,32]. If autonomy is viewed as the strict respect for individual preference, VUS should be disclosed to patients if they wish. However, if in order to exercise their

autonomy, a person needs to have meaningful options, non-disclosure of VUS can be justified:

> '*Choices must be meaningful to be worthwhile. If they are not… autonomy becomes an empty concept*'[25]
>
> '*It does not seem to threaten a person's present or future autonomy to refuse information about test results that are not accurate or actionable*'[26]

Three publications argued that disclosure of VUS could be seen as undermining patient autonomy[25,26,30]:

> '*Dumping data or inaccurate information on people is not making them knowledgeable… When no alternative treatments or actions are available, knowing does not increase autonomy… conveying information without the request of the person is a type of paternalism*'[26]

The status of VUS as medical information

Fourteen publications discussed that the extent to which a VUS can be regarded as useful information was important in deciding on disclosure[14,23,25-30,35,37,39-42]. This distinction was particularly important in publications which considered that having a meaningful choice was a prerequisite of autonomous decision-making. Four publications considered VUS to have a status as medically relevant information[24,27,36,43] (for one publication this was in the context of a head-to-head discussion article[24]):

> '*While [VUS] often create difficult and complex counselling situations, they are health-related information that has the potential to be relevant to the well-being of the tested individual*'[24]

Four publications argued that it is inappropriate to treat VUS as meaningful health-related information[25,26,39,40]:

> '*If return of results fails to meet the twin requirements of reliability and responsible context of return, we simply spew unreliable information… and create a false aura of reliability around results that we actually do not understand*'[40]
>
> '*Such information should not be part of the primary clinical record… providers should not waste time discussing it with patients*'[39]

Most publications discussed that a proportion of VUS will turn out to be relevant to health in the future. Fourteen publications discussed that for some VUS, disclosure may therefore have future benefits[14,24-28,30,32,34,37,39,40,42,43]. However, it is not possible to tell in advance which VUS these benefits will apply to:

> '*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*'[42]

A deciding factor for four publications in determining whether information could be considered clinically useful was whether it was 'actionable' or not (i.e. whether knowing about a variant would give a patient access to options that had not previously been available)[26,28,39,40]:

> '*[The decision to disclose] should focus on the provision of meaningful (i.e. interpretable) information that could lead to concrete health-related preventive or therapeutic measures*'[28]

However, the concept of 'actionability' was not tightly defined – some publications gave examples such as when identification of a variant led to access to preventative treatment, but it was not clear whether more minor 'actions' such as tracing a VUS through a family to help interpret it, would justify disclosure from the perspective of these publications.

The risk of personal and societal harm

Twenty-three publications explicitly discussed the concern that disclosure of VUS could cause harm on an individual patient level[14,23-38,42-47] (those that did not were generally discussing VUS identified in the context of public health screening, or research studies[39-41]). Broadly speaking, the harms anticipated either related to psychological distress, or to inappropriate medical management arising from misinterpretation of the VUS.

Twenty publications mentioned that disclosure of VUS could cause psychological distress, with anxiety the most commonly cited concern[14,23-28,30-32,34-38,42-45,47]. Six referenced research suggesting that disclosure of VUS in the context of pregnancy led to continued worry after delivery and regrets

about having the test[14,27,31,32,34,37]. However, for five publications, although anxiety and distress were described as anticipated outcomes of VUS disclosure, the authors explicitly stated that concerns about psychological harms were not sufficient grounds to withhold VUS from patients[23,24,27,28,36]:

> '*Medical information is often disturbing, but this is usually not considered a reason not to tell the patient about her medical status*'[23]
>
> '*As providers we need to assume responsibility for [parental anxiety] by providing expert counselling and support for the families we are caring for, rather than hiding this information*'[24]

Five publications discussed that disclosure of VUS could lead to inappropriate clinical management, for example unnecessary screening or surgery[29,42,43,45,46]. Eleven publications explicitly discussed that disclosure of VUS in the context of pregnancy could lead to termination of pregnancy on the basis of variants that may turn out to be benign[14,24,25,27,32-35,37,46,47]:

> '*Data might cause more harm than good. Because timely analysis might not be feasible, abortion could seem reasonable to parents who wish to avoid having an unhealthy baby [and] could ultimately… prevent rather than enable the birth of healthy babies*'[33]

There was some discrepancy in how this was viewed: whilst some publications considered this to be a strong argument for non-disclosure (or for not doing a test that could generate VUS in the first place), others took the stance that the role of prenatal diagnosis is to facilitate patient choice, rather than to promote the birth of healthy babies, so did not consider this to be a legitimate argument against disclosing VUS:

> '*a result of uncertain significance is still information… If a woman chooses to avoid the birth of a child with a possible disability when confronted by uncertainty, then this is a legitimate exercise of her reproductive autonomy, just as when she chooses to terminate a pregnancy because of uncertainty about her own social circumstances*'[27]

Considering the question of harm at a societal level, six publications discussed that disclosure of VUS would represent a drain on healthcare and research resources[23,38-40,42,46]:

> '*The process of fully assessing the significance of each [variant identified via genome sequencing] would consume far more time and resource than could possibly be devoted to it*'[46]

However, four publications discussed that if VUS were not made available to patients now, they may have no mechanism to access this genomic information at a later date, and may be less likely to seek an updated genetic opinion in the future[34,37,42,43]:

> '*If these VUS are not made available… the vast majority of participants are not likely to have access to this genomic information through other means until the cost of genetic testing and analysis decreases significantly more*'[43]

Handling uncertainty and the hope of resolution

Four publications discussed that uncertainty can be considered a normal and expected outcome of medical investigations[30,32,41,46]. Two suggested that rather than trying to avoid uncertainty by not disclosing VUS, an alternative approach would be to embrace uncertainty as a legitimate outcome[30,32]:

> '*We need to do more to step away from any ideology around uncertainty eradication; and re-frame uncertainty from something that is intuitively negative to something that is appraised (or managed) in a more value-neutral way*'[30]

Uncertainty was described as being linked to positive concepts such as opportunity and optimism, though often these related to the expected eventual resolution of the uncertainty. Two publications described that disclosure of VUS had the potential to facilitate better public understanding of the limitations of genetic testing[23,48]:

> '*It has been suggested that [unrestricted disclosure of genetic variants found via research] may in a broader sense even educate the general public about biomedical research – including the complexity, ambiguity and occasional meaninglessness of many genetic findings*'[23]

Eight publications discussed the importance of efforts to resolve uncertainty in the longer term, for example via data sharing or review by an expert committee[24,25,31,35,41,44-46]. Ten publications raised concerns about how to manage the situation if scientific uncertainty regarding a VUS is later resolved[14,29,31,38-42,45,46]. They raised questions about whose responsibility it was to seek updated information on VUS as time went by (patient, clinician or laboratory), or whether it would be ethically

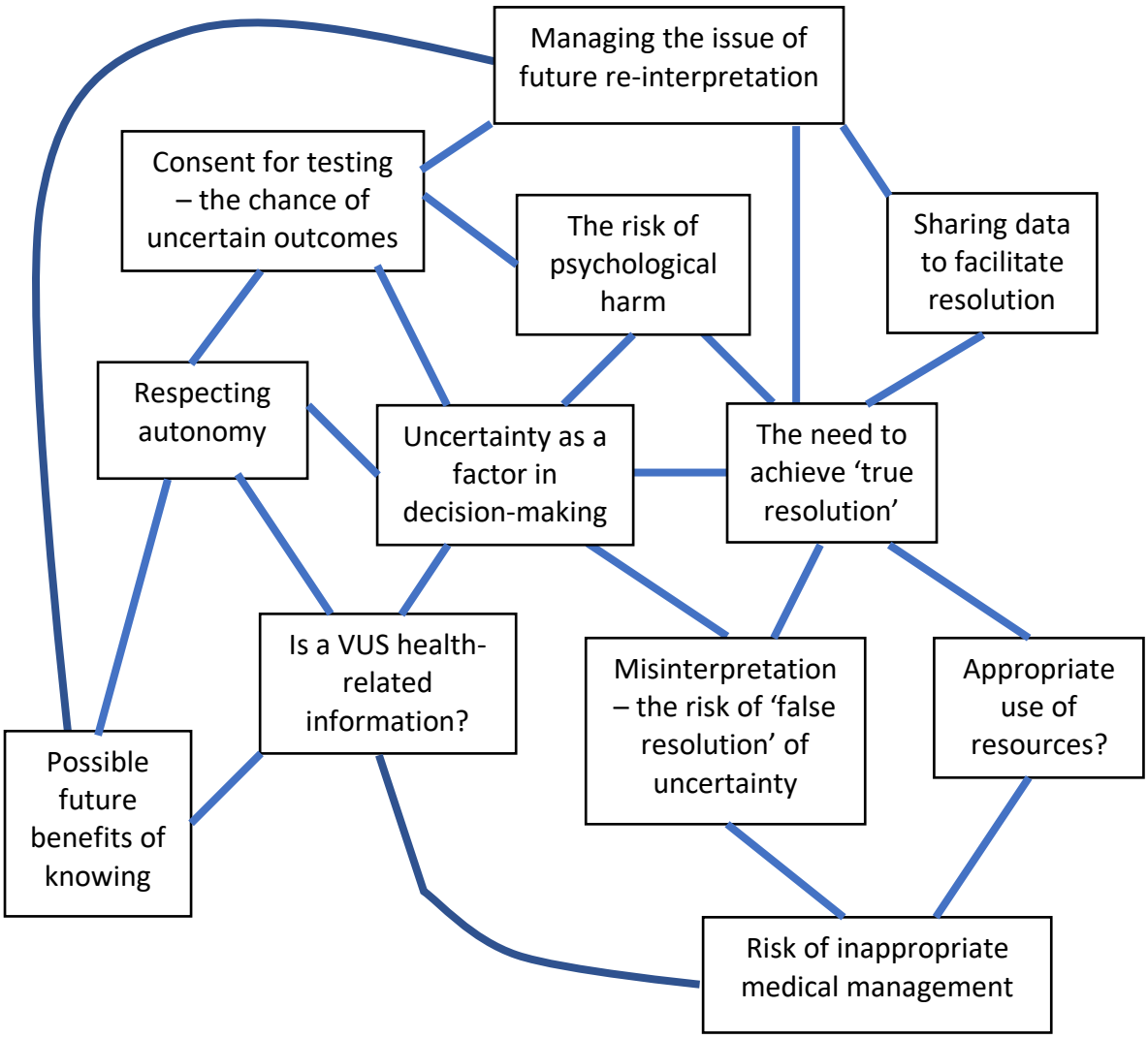
appropriate to re-contact patients if VUS identified in a prenatal context were later reclassified.

Most publications discussed the importance of acknowledging the chance of uncertain outcomes at the outset of testing. Thirteen publications explicitly stated that the possibility of VUS should be discussed as a central part of the consent process[14,25,27,28,30-32,34,35,37-39,46]. Eight publications discussed that the risk of VUS generation should be considered as part of the test selection process[24,25,27,32-35,45]. However, eight publications argued that given the enormous variety and complexity of potential outcomes from broad genetic testing, expecting the consent process to comprehensively cover every aspect of this may be unrealistic[14,25,27,31,32,34,35,38].

Six publications discussed a possible role for a contract between participant and provider regarding whether VUS would be disclosed or not[23,25,30,32,34,35]. However, two publications explicitly acknowledged that even if this had been agreed in advance, deciding thresholds for disclosure could still be ethically challenging[28,35]:

> '*For a test that leads to a near infinite number of possible outcomes, deciding beforehand what one might want to know about will be impossible in all but a very generalised way*'[35]
> '*Which information is certain enough to be disclosed?... what is an acceptable level of uncertainty and should professionals or members of the screened population be the ones to set it?*'[28]

Figure 3: Infographic to show themes identified from the included publications



Discussion

This review aimed to delineate the ethical arguments surrounding whether to report and disclose VUS identified via genetic testing. The arguments identified related to the need to consider the potential impact of VUS disclosure on patient autonomy, whether VUS can be seen to have a status as medical information, the risk of personal and societal harm arising from VUS disclosure or non-disclosure, and the handling of uncertainty and the need for resolution. The findings demonstrate the challenge of reaching a decision on VUS reporting and disclosure, and raise aspects to consider when faced with this decision on an individual patient basis. It remains unclear whether VUS should be disclosed or not, but finding a yes/no answer to a normative question is beyond the scope of a systematic review of reasons[16], and for such a complex question it is unlikely that an overarching conclusion regarding reporting and disclosure will be applicable to every case.

However, this research illustrates the escalating need to develop strategies to manage VUS, with most publications having been published in the last decade. This likely reflects that the issue of VUS has been amplified with the introduction of exome and genome sequencing, and patients and clinicians are being confronted by the identification of VUS on an increasingly regular basis[49]. During the last decade, we have also learnt more about the wide range of normal human variation, with the development of databases that aim to catalogue this, such as ExAC and GnomAD[50]. This has heightened our caution about declaring variants to be pathogenic, with an increasing move towards a stance that variants identified by genomic testing should be 'innocent until proven guilty'[51].

This review highlights the differing contexts in which VUS present a problem. Prenatally-identified VUS emerge as a particularly pressing issue, with a substantial proportion of the included publications focusing on VUS found in this context. The prenatal setting is perhaps particularly difficult because unlike for many other VUS, there is no time to wait for uncertainty to naturally resolve. Decisions regarding disclosure need to be taken under time pressure, and a potential role for uncertainty in decision-making has to be considered. The consequences of disclosure may be large, for example potentially leading to termination of pregnancy.

The impact of VUS disclosure on autonomy was identified as a key theme from this research, but the relationship between disclosure decisions and respect for autonomy was complex. A few publications felt that respect for patient autonomy mandated disclosure of VUS, where others felt that reflexively conveying information of uncertain accuracy could also be seen as a form of paternalism (in deciding that a patient 'needs to know' this information, without considering whether they might want to know). This raises questions about the status of uncertain information. However, people frequently make major decisions based on uncertain information, for example signing up to a mortgage without being certain what their income will be for the next thirty years, suggesting that in some spheres we are accepting that people can make decisions on the basis of uncertainty. Within genetics, it is also relevant to consider that even clearly disease-causing genetic variants can have inherent ambiguity, for example a proportion of women with disease-causing *BRCA* variants will not go on to develop breast or ovarian cancer[52].

However, whether the identification of a sequence variant in itself amounts to medical information at all is up for debate – the majority of variants identified by genomic testing will turn out to be benign[3]. A number of publications cast doubt on the status of VUS as medical information, suggesting that whilst genetic variants remain uncertain, they are not meaningful, and knowledge of them does not open up opportunities or provide explanations for patients. It can be considered that the meaning of a result comes not from technical identification of a variant, but from the lived experience that the variant gives rise to (or has the potential to give rise to) in a particular person. As such, VUS can be considered to be background 'noise' from testing that may one day become clearer, as opposed to medical information in any helpful sense.

The concern about the potential to cause harm by disclosing VUS was very evident from review of the literature. The potential for psychological harm was frequently outlined, although a number of publications made the point that medical information is often distressing or has uncertain implications for a patient and their future, and in other contexts (for example cancer diagnosis) this is not considered a legitimate reason to withhold the information. However, in applying this argument to support disclosure of VUS, this presumes that VUS have a status as medical information.

The need for longer-term resolution of VUS was discussed throughout the publications, demonstrating the current uncomfortable situation where we can generate huge volumes of sequence data, but with significant doubt about what much of it means[49]. Many publications expressed a hope that as our understanding of genetics increases, the problem of VUS will diminish. However, this raises its own ethical issues – for example as VUS become reclassified as clearly pathogenic or clearly benign, how should we react to this and is there a responsibility to monitor the changing status of previously identified variants? Looking at potential solutions to this problem was beyond the scope of this review. However, the issue of VUS and the issue of re-contact are clearly linked, and some arguments for disclosure of VUS would be undermined if we had robust means to periodically re-examine genetic sequence data and re-contact patients in the future if improved genetic knowledge led to identification of pathogenic variants that would previously have been described as VUS.

A further theme that was identified from a subset of the literature was a potential opportunity to embrace uncertainty, recognising that it can have positive aspects as well as negative attributes. Many publications strongly asserted that the possibility of uncertain findings needs to be discussed with patients before commencing genetic testing, with several publications warning that often patients have genetic testing in an attempt to achieve certainty and so are particularly vulnerable to being blindsided by uncertain results. However, by some publications, disclosure of VUS was seen as a potential opportunity to educate patients and the general public that uncertain genetic results are normal and to be expected.

One approach could be to communicate all VUS, fully acknowledging of our inability to interpret them at present and recognising that this will be the case for everyone to a greater or lesser degree. However, taken to the extreme, the lower the threshold for disclosing VUS, the less meaningful a test result becomes, and there is a danger of pathogenic variants with clear implications for clinical care being drowned in a swamp of unfiltered data. At the other extreme, one could decide to only communicate well-understood variants that are clearly relevant to the clinical question being asked. Whilst this avoids the potential harms of unrestricted disclosure, it misses an opportunity to capitalise on the potential good that can be achieved from genomic testing, and without sharing variants and observing the natural history of the patients who carry them, how can we expect to ever learn whether the variants affect health or not?

Limitations

Some relevant publications may not have been captured by the search strategy due to the choice of including ‘genetics’ in the search terms. For pragmatic reasons, this research did not examine grey literature discussing VUS reporting and disclosure such as blog posts, and excluded publications not written in English. This means that the searches performed may have missed a number of relevant publications, and accordingly some ethical arguments regarding reporting and disclosure of VUS may not have been elicited.

A further limitation is that screening of the search results was undertaken by only one person. This had the potential to introduce bias in application of the filtering criteria, and increased the chance of relevant publications being excluded due to human error. Screening of the search results by a second independent researcher would increase confidence in the findings of this research. A similar limitation is that most data extraction was also undertaken by one person. This will have increased the chance of bias in noting of arguments and extraction of themes, and the research would have been enriched by independent extraction of data from all included publications by a second person, then discussion to arrive at a consensus on the themes identified. This was not possible in the context of this dissertation, but independent data extraction from 10% of the publications was undertaken by a second person (my primary supervisor) in order to mitigate this risk, prior to discussion of the themes identified from the publications as a whole.

Another issue that arose during this research was the difficulty extracting data from publications discussing VUS in different contexts. In some cases this made it difficult to establish whether particular arguments within a publication related to the issue of reporting and disclosure of VUS, or whether they pertained to the context in which the VUS was obtained (for example, in publications discussing VUS identified via research, it could be challenging to work out whether an argument against disclosure was because a variant was of uncertain significance, or because the variant had been identified in a research study as opposed to being found via a clinical test). A further concern in interpreting the findings of this research is that the most commonly presented arguments surrounding

an ethical question are not necessarily the strongest, and there is a danger that in trying to examine normative literature in an empirical way this nuance may be lost[53].

Implications for practice and policy

This systematic review of reasons adds to existing research by collating the ethical arguments relating to reporting and disclosure of VUS. It demonstrates the difficulty and complexity of decisions regarding VUS reporting and disclosure, and shows that as well as appraising VUS from a technical scientific perspective, ethical aspects should also be considered in disclosure decisions. With the widespread adoption of the ACMG guidelines for variant interpretation, steps have been made towards reaching technical consensus in how to classify genetic variants[54]. As we move towards mainstreaming genomic testing, we now need to debate how to respond to the variants that we currently cannot classify. Eliciting the perspectives of patients and providers of genomic tests on this issue will be an important next step in helping determine where our thresholds for disclosure should lie in order to responsibly realise the benefits of genomic testing.

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Appendix

Supplementary figure 1: data extraction proforma used for included publications

Date reviewed	
First author	
Journal	
Year published	
Country of corresponding author	
Type of article	
What context of discussion? (research, prenatal, etc)	
Arguments for reporting and disclosure of VUS	
Arguments against reporting and disclosure of VUS	
Arguments that caution about reporting and disclosure of VUS	
Other ethical issues relating to VUS?	

Supplementary table 1: Table to show characteristics of publications which proceeded to data extraction

First author	Year published	Country of corresponding author	Type of publication	Context in which VUS discussed
Berg(39)	2011	USA	Discussion paper	Screening/public health
Bertier(44)	2016	Canada	Systematic review	Use of broad genomic testing
Bredenoord(23)	2011	Netherlands	Discussion paper	Return of research results
Bui(24)	2014	Sweden	Discussion paper	Prenatal testing
Burke(38)	2016	UK	Discussion paper	Use of broad genomic testing
Cheon(45)	2014	USA	Discussion paper	Use of cancer panels
Clarke(46)	2014	UK	Discussion paper	Use of broad genomic testing
De Jong(25)	2014	Netherlands	Discussion paper	Prenatal testing
Evans(40)	2012	USA	Discussion paper	Return of research results
Hofmann(26)	2016	Norway	Discussion paper	Incidental findings of uncertain significance
Jamal(41)	2017	USA	Patient opinions	Use of broad genomic testing
Lazaro-Munoz(43)	2017	USA	Discussion paper	Return of research results
McGillivray(27)	2012	Australia	Discussion paper	Prenatal testing
Mikhaelian(47)	2013	USA	Healthcare professional opinions	Prenatal testing
Moret(28)	2015	Switzerland	Discussion paper	Screening/public health
Moret(29)	2016	Switzerland	Discussion paper	Incidental findings of uncertain significance
Newson(30)	2016	Australia	Discussion paper	Use of broad genomic testing
Quinlan-Jones(31)	2016	UK	Patient, healthcare professional, and laboratory professional opinions	Prenatal testing
Richardson(32)	2017	USA	Discussion paper	Prenatal testing
Shkedi-Rafid(14)	2016	UK	Healthcare professional opinions	Prenatal testing
Shuster(33)	2007	USA	Discussion paper	Prenatal testing
Stark(34)	2013	Australia	Discussion paper	Prenatal testing
Vears(42)	2017	Belgium	Laboratory professional opinions	Use of broad genomic testing
Wellesley(35)	2013	UK	Discussion paper	Prenatal testing
Wertz(36)	1991	USA	Healthcare professional opinions	Prenatal testing
Westerfield(37)	2014	USA	Discussion paper	Prenatal testing