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REVIEW

What's in a name? Justifying terminology for genomic findings beyond the initial test indication: A scoping review

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ABSTRACT

Genome sequencing can generate findings beyond the initial test indication that may be relevant to a patient or research participant's health. In the decade since the American College of Medical Genetics and Genomics published its recommendations for reporting these findings, consensus regarding terminology has remained elusive and a variety of terms are in use globally. We conducted a scoping review to explore terminology choice and the justifications underlying those choices. Documents were included if they contained a justification for their choice of term(s) related to findings beyond the initial genomic test indication. From 3571 unique documents, 52 were included, just over half of which pertained to the clinical context ($n = 29$, 56%). We identified four inter-related concepts used to defend or oppose terms: expectedness of the finding, effective communication, relatedness to the original test indication, and how genomic information was generated. A variety of justifications were used to oppose the term "incidental," whereas "secondary" had broader support as a term to describe findings deliberately sought. Terminology choice would benefit from further work to include the views of patients. We contend that clear definitions will improve ethical debate and support communication about genomic findings beyond the initial test indication.

Introduction

Advances in genomic sequencing technologies have enabled the routine generation of vast amounts of genetic data and information, including findings beyond the initial test indication.[1] This phenomenon is not new to clinical or research settings.[2,3] In both settings, an array of terms are used to describe these types of genomic findings. Aside from

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"incidental," descriptors include "secondary," "unsolicited," "unexpected," "unsought for," and "additional," to name a few. These terms are used interchangeably and inconsistently in the literature and in practice, often with little clarification or justification.[4]

Much of the original debate about terminology was prompted by the publication of the American College of Medical Genetics and Genomics (ACMG) 2013 guidelines on the reporting of incidental findings, as they were called at the time. The ACMG stipulated that any clinical genomic test be accompanied by intentional analysis of 56 "clinically important" genes.[5] Following publication, extensive discussion ensued regarding the appropriateness of using "incidental" to describe deliberately sought findings. The ACMG later adopted "secondary" in a subsequent version of the policy.[6]

It is now a decade since the initial publication of the ACMG guidelines. Yet, inconsistent use of terms for these findings continues.[7] This lack of consensus within the genomics community as to the naming and designation of findings impedes constructive discussion about how they ought to be managed.[7] Reasons underlying the choice of terms are often unclear but may reflect differences in the perception and prioritization of underlying definitional concepts.[8] A lack of clarity engenders confusion, increases the likelihood of miscommunication between stakeholders and hinders progress toward professional consensus guidelines.[9] As integration of genomics into routine medicine advances, developing agreed-upon terminology is crucial to deliberate meaningfully about ethical management of genomic findings beyond the initial test indication.[10]

To inform a consistent approach to the management of such findings, it is first necessary to explore existing reasons given in the literature for terminology choice. We therefore undertook a scoping review to systematically identify and describe the justifications ascribed to various terms for genomic findings beyond the initial test indication. We sought to answer three research questions:

1. What justifications or reasons underlie the choice of terms used in the literature to describe genomic findings beyond the initial test indication?
2. What terms typically accompany these justifications or reasons identified in the literature?
3. What contextual factors, such as setting (eg, clinical or research) or age/population group (eg, pediatric or adult populations) influence justifications or terms used within the literature?

Materials and Methods

We conducted a scoping review guided by the Joanna Briggs Institute evidence synthesis manual, which builds upon the scoping review framework set out by Arksey and O'Malley.[11] We selected a scoping review over other methods of evidence synthesis because we aimed to explore justifications for terms, rather than evaluate their effectiveness.[12] Reporting items align with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for scoping reviews.[13] No similar reviews were identified on International Prospective Register of Systematic Reviews, Joanna Briggs Institute Systematic Review Register, Medline, or Cochrane Reviews. An a priori review protocol is available on the Open Science Framework (https://tinyurl.com/2kh2ca5b). The original protocol included an objective to develop a position statement about terminology use. However, the justifications identified in this review had varying degrees of soundness. We concluded that an evaluation of these justifications, in view of developing a position, would require separate analysis and evaluation with broad stakeholder input. Additionally, we initially planned to assess the role of geography in terminology choice. We ultimately removed this from our aims because (among other reasons) the review was designed to primarily capture justifications rather than provide a representative illustration of global terminology use.

Eligibility criteria

Using the population, concept, and context criteria, we sought documents that defined and justified terms related to genomic findings beyond the initial test indication (see Supplemental Information for full details).[12] Briefly, we included documents that provided reasons for and/or against terms (ie, a justification for the choice of a particular term) and pertained to the clinical or translational research context. Documents published before 2010 were excluded because the likelihood of generating genomic findings beyond the aim of the initial test was low before the mainstream uptake of comparative genomic hybridization that occurred around this time.[14]

Search strategy and information sources

In consultation with an information scientist, we searched MEDLINE, EMBASE, Web of Science, and Google Scholar. Medical Subject Heading terms and keywords were combined with Boolean operators, such as "incidental*" or "secondary finding," "human genetics" or "genomics," and "terminology as topic" (see Supplemental Information for full search strategy). The aim of our search was to explore the literature for justifications accompanying terms in use. Therefore, we did not limit the review to any particular terms. Results were limited to the English language. The search was last run on June 6, 2022. Forward and backward searching was performed on all documents meeting eligibility criteria. Using Web of Science, we generated a list of citations that included (1) references that had cited eligible documents and (2) references in the bibliographies of eligible documents.

Eligibility screening

Citation files were downloaded from databases into the reference management tool, Zotero, and deduplicated.[15]

Eligibility criteria were piloted by two reviewers (S.W. and K.L.) on 20 randomly selected documents. Minor refinements were made, such as specifying that documents related to prenatal genomic testing were eligible.

Title and abstract screening

Citations were uploaded into Covidence (systematic review software) for title and abstract screening.[16] Documents were deemed eligible if they met inclusion criteria, required further reading to determine eligibility, or had missing or ambiguous information. Two reviewers (S.W. and K.L.) independently screened 20% of the documents in tandem. A Cohen's kappa statistic of 0.88 was achieved before the reviewers independently screened the remainder.[17]

Full-text screening

Citations were downloaded from Covidence into Microsoft Excel. Three reviewers (S.W., M.H., and K.L.) independently screened 10% of the full-text documents in tandem. A Fleiss-kappa statistic of 0.87 was achieved before each reviewer continued to screen independently.[18] Disagreements about eligibility were resolved through discussion among the core review team (S.W., M.H., K.L., and A.J.N.).

Data items and charting

Predetermined data items were charted in Microsoft Excel (see Supplemental Information for the full list of data items). Briefly, we charted documents details (eg, author, title, year, and country), setting (eg, clinical, translational research, or unspecified research), and age/population group (eg, pediatric, adult, and prenatal). We extracted the justifications used for terms verbatim. Two reviewers (S.W. and M.H.) piloted the data charting workbook with 25% of eligible documents, resulting in removal of items that were not consistently reported (eg, whether there was mention of the pathogenicity or actionability of variants). After piloting, one reviewer (S.W.) charted independently, and these were checked for accuracy by another reviewer (K.-J.L.).

Data mapping and synthesis

We inductively mapped the justifications used for and against terms and conducted a narrative synthesis.[19] We developed a preliminary synthesis by organizing data into tables that grouped together the same preferred term. For example, all documents supporting the term "incidental" were grouped with the various justifications noted alongside. A second set of tables combined the same or similar justifications with the accompanying terms and contextual factors (ie, setting and age/population group) noted alongside. Tables captured justifications for and against terms.

We then explored relationships within our data by visualizing the number and type of justifications and terms, as well as determining whether there were dominant contextual factors for the justifications. We defined a dominant contextual factor as appearing in >50% of the same group of justifications and incorporated these observations into the narrative synthesis. Because our review was designed to explore justifications and accompanying terms, we did not apply statistical analyses to the observed justifications, terms, or contextual factors.

Justifications were grouped into similar concepts (eg, "expectedness of the finding" or "effective communication"), and these groupings were used to organize the narrative summary. In addition, the narrative synthesis involved iterative and collaborative critical reflection. Regular meetings among the core review team provided an opportunity to discuss our interpretations of the data by drawing on our multidisciplinary knowledge, which included ethical, legal, and social issues in genomics, evidence synthesis methodology, policy, genetic counseling, and philosophy.

Results

Fifty-two documents were included (Figure 1). Many of these were from the United States (n = 18, 35%), set in the clinical context (n = 29, 56%), and applied to both adult and pediatric populations (n = 26, 50%). Almost half were normative documents (n = 25, 48%), defined here as conceptual, nonempirical papers that "provide arguments in support of [a]… preferred view of how things ought to be."[20] Of the empirical articles reporting primary data (n = 10, 19%), one reported patients' perspectives about terminology and one reported clinicians' perspectives.[21,22] In the remaining majority (n = 50, 96%), justifications for terminology were based on the authors' views and beliefs. Table 1 summarizes the document characteristics.

We identified justifications for and against a variety of terms. A high degree of overlap meant that in many cases, the same justification was used to argue for or against different terms and the same terms were ascribed to different justifications (Table 2). Four main concepts capture the justifications: "expectedness of the finding," "effective communication," "relatedness to the original test indication," and "how genomic information was generated."

Expectedness of the finding

A prominent concept invoked in justifications for and against a variety of terms was whether results can be expected or anticipated. Most commonly, "incidental" was opposed because genomic technologies are known to generate findings beyond the initial test indication.[23-34] "Unexpected,"[23,31,35,36] "unsought for,"[37-39] "unanticipated,"[37,40] "chance findings,"[35] and "secondary"[31] were also opposed on this basis. "Unanticipated" was specifically opposed in one document on the basis that the frequency of

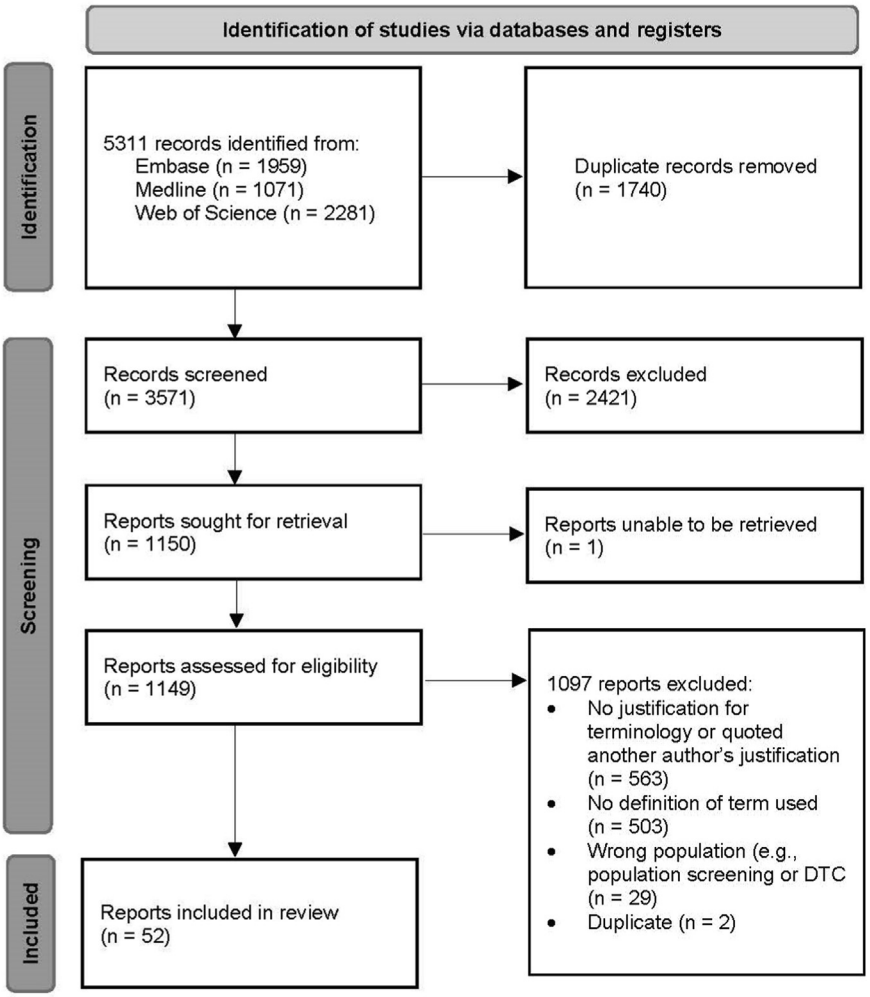

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.[13] From 3571 unique records, 52 were included in this review. DTC, Direct-to-consumer.

some findings can be estimated based on population frequency.[37] Further opposition to "unexpected" was based on the variable extent to which different genomic findings can be expected[41] and that the term could cast doubt on the clinician's competency.[37] A prominent argument, often given in response to the 2013 ACMG guidelines on incidental findings,[5] was that "incidental" is ill-suited to describe findings that are actively and intentionally sought.[6,26,27,29,37,39-52]

Instead, many documents proposed that terms should convey our ability to anticipate genomic findings that are beyond the initial test indication. Supported terms included "secondary,"[22,53] "unsolicited,"[23,28,31,39,54] "additional,"[23,29,34,55] "known unknowns,"[30] and "unanticipated."[25] There was prevalent support for "secondary" findings to describe results arising from the deliberate effort to uncover pathogenic variants outside of the original test indication.[6,29,42,53,56-58]

Some suggested "incidental"[42,43,58] and "individual genomic result"[27] as umbrella terms to broadly refer to findings that could and could not be anticipated. A minority supported terms to describe findings from genomic testing that could not be reasonably anticipated, including "incidental,"[22,43,53] "unsolicited,"[57] and "off-target results."[37] In the prenatal setting, "incidental" was applied to findings identified in parents because "incidental," it is argued, means "a diagnosis found unintentionally."[60]

Effective communication

Some documents were guided toward developing widely accessible terminology. For example, "incidental" was commonly justified on the basis that it is the most often used and universally understood term.[40,48,62,63] A term not being well recognized (eg, "secondary"[59] or "unrelated"[40]), having a negative connotation (eg, "opportunistic"[40]), or having potential to cause confusion (eg, "incidental"[21,32,57,60] or "unrelated"[37]), were cited as reasons to avoid their use. Others supported terms such as "unanticipated"[26] and "additional"[21,41] because of their familiarity to patients. Several authors opposed terms such as "unrelated,"[40] "incidental,"[48] and "unexpected"[41] because the term was unable to fully capture the concept they were trying to convey.

Table 1 Article characteristics ($N = 52$)

Article Characteristic	*n*	%
First author country		
United States	18	35
The Netherlands	9	17
United Kingdom	7	13
Belgium	6	11
Canada	5	10
Germany	4	8
France	2	4
Japan	1	2
Setting		
Clinical	29	56
Both clinical and research	14	27
Translational research	6	11
Unspecified research	3	6
Methodology		
Normative	25	48
Qualitative	5	10
Guideline	5	10
Nonsystematic review	5	10
Quantitative	4	7
Meeting report	4	7
Systematic review	2	4
Mixed-methods	1	2
Case study	1	2
Age/population group		
Both adult and pediatric	26	50
Not specified	16	31
Adult	6	11
Prenatal	3	6
Pediatric	1	2
Primary focus on terminology		
No	44	85
Yes	8	15

Another common reason used to justify terms was their inclusion in guidelines relevant to the authors' context.[6,28,40]

In both clinical and research settings, authors argued against terms they thought misrepresented the importance of genomic findings to patients or research participants. For instance, "incidental"[21,32,37] and "secondary"[40] were thought to minimize the significance of a genomic finding. Terms such as "unrelated,"[37] "unanticipated,"[37] and "incidental"[61] were rejected because they do not help patients or research participants understand what kind of results they may receive. Furthermore, "unexpected" was deemed inappropriate because of patients' expectations that anything of clinical significance be communicated to them.[37] Conveying the importance of a genomic finding to patients or research participants was thought to be achieved with "additional,"[21] "unsolicited,"[57] and "unanticipated."[26] Some preferred "additional" because they thought it did not convey a positive or negative value.[21,41]

Relatedness to the original test indication

A common justification for terminology choice, often in the clinical setting, was the ability to convey the finding as unrelated to the patient's clinical presentation or test indication. Many authors justified their terminology choice on this basis, highlighting that "incidental,"[60,64] "unsolicited,"[33,39,54,57] "additional,"[41,55] "unexpected,"[51,60,61] and "unanticipated"[25] all fulfilled this criterion.

Some authors thought that a term's ability to establish a link between the primary result and the finding beyond the initial test indication was important. Terms such as "secondary"[37] and "additional"[21] were supported on this basis, whereas "unsought for"[37] and "unexpected"[41] were rejected. Others rejected terms such as "primary" and "secondary," arguing that selecting terms based on establishing a relationship between findings is irrelevant.[49]

How genomic information was generated

Justifications based on how genomic findings were generated were used to argue both for and against terms. For example, terms such as "unsought for"[37,38] and "incidental"[26] were rejected on the basis that they did not convey the amount of effort required to identify and interpret a genomic variant. "Unanticipated" was offered as a term that did not belittle the clinician's or researcher's expertise or effort required to generate a finding beyond the initial test indication.[26]

In the earlier years of its clinical application, some commentators conceived of genomic testing as a form of screening, rather than simple diagnostic testing. To reflect this distinction, "unsolicited"[33,39] and "genome-wide screening with a diagnostic indication"[35] were offered as appropriate terms.

Others wanted to move away from terms that emphasized the way findings were generated and focus instead on the result at hand. Support for "individual genomic result" was thought to achieve this because this term does not communicate the primary intention of the clinician or researcher.[27] Meanwhile, "incidental" was thought to place too much emphasis on the clinician's or researcher's intention, rather than the nature of result.[27,38] Others supported terms that simply describe a finding that should be disclosed, suggesting "research findings" as a suitable alternative.[49]

Discussion

In this review, we identified and described justifications for and against terms used to refer to genomic findings beyond the initial test indication. Justifications were grouped into four conceptual domains, namely the expectedness of the finding, effective communication, relatedness to the original test indication, and how genomic information was generated. Conceptual overlap was evident between domains, individual justifications, and accompanying terms.

The many and varied justifications opposing "incidental" ranged from normative arguments (eg, the idea that clinicians ought to be prepared for any possible finding)

Table 2 Summary of justifications, terms, and citing authors

Justification	Term
Expectedness of the finding	
Justifications against terms	
Inappropriate because findings can be anticipated	Incidental[23-34] Unexpected[23,31,35,36] Unsought for[37-39] Unanticipated[35,40] Chance findings[35] Secondary[31]
The frequency of some findings can be estimated based on population frequency	Unanticipated[37]
The extent to which a finding is unexpected can vary widely	Unexpected[41]
Casts doubt on the health professionals' competency to anticipate findings	Unexpected[37]
Inaccurate to describe findings that are actively and intentionally sought (but outside aim of original test indication)	Incidental[6,26,27,29,37,39-52]
Justifications for terms	
Conveys that these findings can be expected (ie, that "beyond scope" results may be generated)	Secondary[22,53] Unsolicited[23,28,31,39,54] Additional[23,29,34,54,55] Known unknowns[30] Unanticipated[25]
Conveys that there has been a deliberate search for clinically important findings	Secondary[6,29,40,53,56-58]
Umbrella terms to refer to findings that can and cannot be anticipated	Incidental[42,43,58] Individual genomic result[27]
Conveys that these findings could not reasonably be anticipated	Incidental[22,43,53] Unsolicited[57] Off-target results[37]
Effective communication	
Justifications against terms	
It is not well recognized	Secondary findings[59] Unrelated[40]
Has a negative connotation	Opportunistic[40]
Has potential to cause confusion	Incidental[21,32,57,60] Unrelated[37]
Minimizes importance of finding to patients and participants	Incidental[21,32,37] Secondary[40]
Does not fully capture the concept	Unrelated[40] Incidental[48] Unexpected[41]
Does not convey what kind of results patients can expect to receive	Unrelated[37] Unanticipated[37] Incidental[61]
Inappropriate because patients expect anything of clinical significance be communicated to them	Unexpected[37]
Justifications for terms	
It is the most commonly used and understood term	Incidental[40,48,62,63]
It is already familiar to patients	Unanticipated[26] Additional[21,41]
It is included in guidelines relevant to authors' context	Incidental[40] Secondary[6] Unsolicited[28]
Conveys the importance of a genomic finding	Additional[21] Unsolicited[57] Unanticipated[26]
Does not convey a positive or negative value	Additional[21,41]

(continued)

Table 2 Continued

Justification	Term
Relatedness to the original test indication	
Justifications against terms	
Does not establish a link with the primary findings	Unsought for[37] Unexpected[41]
Relationship of the finding to original test indication is irrelevant	Primary finding[49] Secondary finding[49]
Justifications for terms	
Conveys that the finding is unrelated to original test indication	Incidental[58,64] Unsolicited[33,39,54,57] Additional[41,55] Unexpected[51,60,61] Unanticipated[25]
Establishes a link between primary result and the finding	Secondary[37] Additional[21]
Process of generating genomic information	
Justifications against terms	
Belittles the effort involved in identifying and interpreting a genomic finding	Unsought for[37,38] Incidental[26]
Emphasizes researchers' intention rather than the nature of the result	Incidental[27,38]
Justifications for terms	
Does not belittle the clinician or researcher's expertise or effort	Unanticipated[26]
Conveys a type of genomic screening, rather than diagnosis	Unsolicited[33,39] Genome-wide screening with a diagnostic indication[35]
Conveys that the finding "meets criteria" for disclosure	Research findings[49]

to issues to do with perceptions of the term itself (eg, the term minimizes a finding's significance to patients). Our review has highlighted the absence of a shared understanding of "incidental," evidenced by variation in concepts underlying justifications for or against its use. We found "secondary" was widely adopted to describe the deliberate search for genomic variants outside of the initial test indication. The interplay between "incidental" and "secondary" primarily centers around the expectedness of the finding, with "incidental" deemed inappropriate because of the known capability of genomic testing to produce findings beyond the initial test indication. Meanwhile, "secondary" was accepted for its ability to convey that these findings would not only be expected but deliberately sought. However, our results may reflect the high proportion of documents pertaining to a North American context; in other regions, deliberate searching is neither routinely endorsed by professional organizations nor commonly executed.[4,33,65,66] Professional genomics organizations could assist the genomics community as they struggle to agree on the meaning of "incidental" and "secondary" by including clear definitions. Alternatively, some organizations have moved away from "incidental" and "secondary,"[33] and this could be influencing clinicians' and researchers' choice of terms.[28] Ensuring that we have a shared understanding of these commonly used terms is critical for future clinical practice, research, and policy guidance.

Inconsistency and ambiguity in the way terminology is used and justified may be explained by the variety of settings within which genomic testing is offered.[67] Different motivations, perspectives, and priorities of stakeholders are underpinned by myriad internal and external expectations of clinicians and researchers. For example, research genomic testing may be aimed at identifying variants with unknown or unclear effects. In contrast, clinical genomic testing is aimed at identifying pathogenic variant(s) in a gene known to be associated with the patient's phenotype. Communicating the relatedness of a finding to the initial purpose of testing may be more important in clinical than research settings. Our review found that terminology choices in the research setting were justified by simply appealing to the term's capacity to describe what was found, as opposed to the clinical setting, where terms tended to be justified based on their relatedness to the primary purpose of testing or how the genomic information was generated.[27,38,49] Indeed, the concept of relatedness to the initial test indication was more prevalent in discussions of naming genomic findings in documents from the clinical rather than research context. It is likely clinicians prioritize terms that help to set patients' expectations by differentiating the possible results from genomic testing.[9] A primary function of pretest genetic counseling is to facilitate client-centered discussions about the implications of genomic testing, including discussions that elicit preferences and facilitate shared decision making about disclosing findings beyond the initial test indication.[68]

Therefore, to help patients navigate consent discussions, terminology that distinguishes between results related to the purpose of testing, and other possible results may help patients to provide informed consent.

An unintended finding of our review was the absence of literature reporting patients' and research participants' perspectives about terminology. Most justifications arose from the perspectives of the document authors, rather than primary data. Although some commentators offered justifications for or against terms based on hypotheses about patients' or research participants' interpretations of terms, only one study obtained and reported empirical data on patients' perspectives.[21] Notably, this study identified a discordance between terms typically used by the genomics community ("incidental") and patients' preferences ("additional"). Balancing the views of expert stakeholders with the voices of patients and research participants is in line with emerging priorities within the genomics community, namely diversity, equity, and inclusivity.[69] In future, studies exploring the impact of genomic findings upon patients and research participants could specifically ask about the perceptions and impact of terminology. Comparing and synthesizing the definitions of terms describing genomic findings would complement this review of justifications. Developing a shared understanding will support the goals of genetic counseling, including effective communication, education, and support in interpreting genomic information.[68]

Strengths and limitations

The concepts described in this review are inter-related, exhibiting some degree of overlap, meaning that justifications may have been synthesized differently by a different team of reviewers. We managed this by critically reflecting upon our assumptions and holding regular team meetings. In addition, the heterogeneity of terms means that it is possible some documents were missed in this review.[7] Because of resourcing, we were only able to include documents written in English but acknowledge that similar and important debates are taking place globally. Justifications for terminology in languages other than English may have provided additional insights. Our search methods were limited to the specified academic databases. As such, except for forward and backward searching, some types of materials (such as book chapters or gray literature) may not have been identified. The review is strengthened by the expertise of our interdisciplinary team and by conducting the review in accordance with established evidence synthesis guidelines.

Conclusion

Our review has highlighted an abundance of justifications used to support and oppose a variety of terms to describe genomic findings beyond the scope of the original test. Justifications were synthesized into four overarching concepts: "expectedness of the finding," "effective communication," "relatedness to the original test indication," and "how genomic information was generated." Our review identified broad opposition to using "incidental" in the genomics context, although reasons for opposing its use vary widely. Different terms may be suited to clinical and research contexts respectively because of their distinct goals and priorities. Future research could use these findings as a conceptual map for stakeholder consultations, which should amplify patients' voices. Developing widely agreed-upon terminology will support effective communication as we move toward a consensus on ethical management of genomic findings beyond the initial test indication.

Data Availability

Data are available upon request by contacting the corresponding author.

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Ethics Declaration

Ethical approval was not sought because this was a secondary analysis of published data. No human or animal participants were involved in this review.

Conflict of Interest

The authors declare no conflicts of interest.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gim.2023.100936) contains supplemental material, which is available to authorized users.

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