Title: Stakeholder views on secondary findings in whole-genome and whole-exome sequencing: a systematic review of quantitative and qualitative studies

Short running title: Stakeholder views on secondary findings in genomic sequencing

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DISCLOSURE

The authors declare no conflict of interest.

ABSTRACT

Purpose: As whole-exome and whole-genome sequencing (WES/WGS) move into routine clinical practice, it is timely to review data that might inform the debate around secondary findings (SF) and the development of policies that maximize participant benefit.

Methods: We systematically searched for qualitative and quantitative studies that explored stakeholder views on SF in WES/WGS. Framework analysis was undertaken to identify major themes.

Results: 44 articles reporting the views of 11,566 stakeholders were included. Stakeholders were broadly supportive of returning 'actionable' findings, but definitions of actionability varied. Stakeholder views on SF disclosure exist along a spectrum: potential WES/WGS recipients' views were largely influenced by a sense of rights, while views of genomics professionals were informed by a sense of professional responsibility. Experience of genetic illness and testing resulted in greater caution about SF, suggesting that truly informed decisions require an understanding of the implications and limitations of WES/WGS and possible findings.

Conclusion: This review suggests that bidirectional interaction during consent might best facilitate informed decision-making about SF, and that dynamic forms of consent, allowing for changing preferences, should be considered**.** Research exploring views from wider perspectives and from recipients who have received SF is critical if evidence-based policies are to be achieved.

Key Words: genomics; secondary findings; ethical, legal, and social issues; genetic counseling; stakeholder perspectives

INTRODUCTION

As genome sequencing moves from the realm of research and difficult-to-solve clinical cases into routine clinical care, so do the wider implications of this technology. In patients or families with a suspected genetic disorder, when single gene or panel testing fails to provide a genetic explanation, genome sequencing is becoming widely available. Whole-genome (WGS) and whole-exome sequencing (WES)—wherein the genome, or the protein-coding parts of the genome, is sequenced in its entirety—might completely replace panel tests in the foreseeable future.

While WES/WGS provides a valuable opportunity to learn about genomic contributions to disease ('primary' findings), it also has the potential to reveal genetic information that may not pertain to the patient's presenting condition—including variants associated with other health conditions, which may or may not be medically actionable, and are unexpected.[1] A variety of terms have been applied to such findings ('secondary', 'incidental', 'additional');[2-4] the term secondary findings (SF) has gained traction and is used here inclusively to cover findings that are not pertinent to the presenting condition, whether detected incidentally or actively sought.

The issue of SF management in WES/WGS has sparked much debate. SF are not new to medicine, but are becoming a more frequent issue in genetics due to more extensive use of WES/WGS in the diagnosis of rare disease and cancer. With each human genome expected to contain approximately 100 genuine loss of function variants,[5] SF in WES/WGS are inevitable. Full disclosure of SF is economically and logistically impractical, but it has been argued that complete non-disclosure is unethical due to the potential benefits of medical intervention for some SF.[6] Current practice in research and clinical settings varies between the two extremes. In 2013, the American College of Medical Genetics (ACMG) put forward recommendations

concerning SF in clinical WES/WGS: active screening of a defined list of genes, in which mutations could imply risk of potentially life-threatening disease, where intervention is available, and in which a long asymptomatic phase may conceal disease expression.[7] The ACMG report suggested that, in all individuals undergoing clinical WES/WGS, there is a moral obligation to report variants of known (or in some cases expected) pathogenicity, interpreting them in the context of the patient's personal and family history. While there is support for the ACMG recommendations, opponents (and alternative guidelines from Europe and Canada) argue for greater caution in the analysis, and return, of such findings.[8-12]

As WES/WGS begins to be implemented in routine clinical practice, such as through the 100,000 Genomes Project currently underway in the UK National Health Service, increasing numbers of patients and their healthy relatives are being recruited. It is therefore timely to collect and review data that might inform this debate, so that WES/WGS initiatives maximize clinical utility and contribute to ethical healthcare delivery.

Commentators have argued that the development of policy around SF needs to consider the views and attitudes of relevant stakeholders, and obtain insights into the factors that have contributed to their formulation.[13] Since the publication of a systematic review on secondary findings in genomics four years ago,[14] which urgently called for research in this area, many empirical studies have been conducted. Due to the contemporaneous collection of these empirical data, SF management policies in WES/WGS have inevitably been unable to make full use of them. To date, we are aware of no systematic review of these studies, therefore, we have collated and synthesized them in order to evaluate the extent to which they might inform policy on secondary findings, and identify areas for further research.

MATERIALS AND METHODS

Literature Search Strategy

We conducted a systematic search for research studies that examined views and preferences towards SF in WES/WGS. The protocol for this review was prospectively registered in an online database.[15] Searches were conducted across six databases and included all literature in the databases from their date of inception to April 2015, with electronic updates included through 1 May 2016 (Figure 1). Search terms for secondary findings (including incidental and additional) were combined with terms for clinical sequencing (genetic, genomic, genome, and exome sequencing) (Figure S1).

Study Selection Criteria

The review included primary research articles based on qualitative (semi-structured interview- and focus group-based) and quantitative (survey and questionnaire-based) methods. Studies were included if they explored stakeholder views and experiences around SF in WES/WGS in a healthcare context, in both clinical and research settings. Articles were excluded if they were not published in English or the citation lacked an abstract. Articles were also excluded if they did not discuss WES/WGS (e.g. discussion limited to chromosomal microarray), or if they did not include (or only included superficial) discussion of secondary findings. Articles that explored views on return of results in a non-healthcare context, such as direct-to-consumer genetic testing, were also excluded. Secondary findings specifically in minors are not discussed as we acknowledge that this raises additional issues and could warrant its own review.

Two authors (MM, EO) independently screened the titles and abstracts of all identified articles against the eligibility criteria, using Covidence systematic review management software (covidence.org). In cases of disagreement, inclusion was resolved at a meeting between the two

reviewers. Both reviewers then screened full text copies of the selected articles, in order to determine final inclusion. Initial screening was followed by reference scanning and snowballing, where the reference of included papers were searched by hand, to find additional articles relevant to the review.

Data Extraction and Analysis

For both qualitative and quantitative studies, a general data extraction form was used that included: bibliographic information, study characteristics, participant characteristics and main findings. Two authors (MM, BF) independently completed the data extraction for each study and MM checked for accuracy and for completeness.

A framework analysis approach was used,[16] where data integration occurred at the point of extraction. The approach was well suited to this review, as it can be applied to mixed methods studies and is particularly useful in multi-disciplinary health research teams.[17] While traditionally applied to primary data, we employed it as a review methodology. This was feasible as the studies investigate the same topics in a manner that can be categorized together.[17]

Initially, MM and EO reviewed six articles (three qualitative and three quantitative studies). Results sections of the qualitative studies were coded in a non-restrictive manner and, combined with analysis of questions asked across quantitative studies, a working analytical framework was produced. This framework was then applied to all of the other studies, where the results sections were coded by MM using NVivo 10 (QSR International), and manually reviewed by EO. Throughout this process, the authors continued to revise the framework in order to reflect the data most accurately. Articles included from electronic updates were each coded by MM and EO and integrated into the pre-existing framework. From the final framework, data was

compared and evaluated to derive a higher order synthesis that goes beyond the content of the included articles.

Critical Appraisal

Each of the studies was assessed using an established quality appraisal system, with a particular emphasis on assessing the comprehensiveness of reporting. In the case of the qualitative studies, we employed the COREQ checklist tool,[18] adapted using the Critical Appraisal Skills Programme (CASP) checklist (Table S2).[19,20] In the case of the quantitative studies, we used checklist tools adapted from Boynton and Greenhalgh[21] and Greenhalgh et al (Table S3).[22] In both cases, MM and BF independently scored articles according to the appropriate checklist after piloting three by consensus. Inter-assessor reliability was measured by calculating Kappa statistics. No quality cut-off was used, but a set of initial screening questions was employed to ensure appropriateness of methodology and analysis, and relevance to synthesis topic.

RESULTS

Systematic Review

A total of 44 published research studies met the criteria for inclusion (Table 1). Of the included articles, 15 employed quantitative methods, 25 employed qualitative methods and four used mixed methods (Table 2). The majority of the studies (72.7%) were from the USA, with the others representing Canadian (13.6%), European (9.1%) and multinational (4.5%) groups of stakeholders.

Study Participants

Accounting for studies reporting on the same participants, the viewpoints of 11,566

unique stakeholders are represented (Table 2). Stakeholders include patients with genetic disorders or cancer diagnosis, relatives, WES/WGS research participants and members of the public (collectively termed 'WES/WGS recipients'); healthcare professionals (HCPs) in genetics or other specialties, both patient-facing and healthcare scientists, primary care physicians, genetics researchers, and IRB chairs ('WES/WGS providers'). Both of these groups include both actual and potential recipients or providers of WES/WGS: participants have a wide range of exposure to genetic disease and genetic testing, from potentially no direct exposure (members of the public) to those who are actively providing or receiving WES/WGS. 34.1% of studies include participants who have 'direct WES/WGS experience' (providing or receiving) together with participants who do not (Table 2). No studies in the review focus on stakeholder experiences with handling or receipt of genomic SF.

Critical Appraisal

Across the studies, quality and comprehensiveness of reporting was highly variable (Table S4 and Table S5): scores for quantitative papers ranged from 8-23 (out of 26), while scores for qualitative papers ranged from 11-19 (out of 32). Although reporting of data collection was weak across the studies, with few qualitative studies reporting the theory underpinning analysis, findings/results were generally well reported. Qualitative studies elicited novel concepts and acted as particularly rich sources of data for the synthesis. Between the reviewers, there was substantial agreement on the scores for both quantitative papers (Kappa score = 0.614, 95% CI [0.538, 0.690]), and qualitative papers (Kappa score = 0.749, 95% CI [0.697, 0.781]).

Thematic Areas

From the framework analysis we identified 10 major thematic areas (Table 3). Illustrative quotations from the primary studies can be found in the Supplementary Material and Methods.

Preferences for secondary findings. An overwhelming majority of stakeholders believe that some form of SF should be returned if identified.[23-45] When measured quantitatively, studies report high desire (95-100%) to receive or return clinically actionable SF[27-29,31-33,38,44,45]— notably, this includes surveys of genetics HCPs.[31,33] The most commonly cited reason for wanting SF was to have the opportunity to act on findings, although the definition of 'actionability' varied. It included the availability of treatment[13,24,33,36,43,46-49] and prevention,[24-26,42] but others endorsed or raised issues such as the ability to plan or alter lifestyle[24,26,27,32,35,42,43,46,50] or influence reproductive decision-making.[25,29,30,32,33,37,46,49,51,52] Over half of stakeholders, of whom the question was asked, desired to receive or return 'all' secondary findings, regardless of actionability (52-100%).[25-28,33,38,39,44] Some cited knowledge as empowering,[25,29,32,42] and many felt a sense of entitlement to this information (detailed further under *Rights and Responsibility).* Of note, while some studies reported that 'all' study participants were interested in receiving some form of SF,[23,25,29] many reported a small proportion of recipients who want only primary findings.[27,28,31,33,38,42,45] Providers did support the return of some SF, however comparative studies found slightly less support for returning SF among genetics HCPs compared to non-genetics HCPs,[33] and among providers with more clinical training.[43,53] These are professionals who interact directly with patients, and might have disclosed, or be in a position to disclose, SF. Support for return of SF with less certainty (including variants of unknown significance) was lower than unambiguously pathogenic variants, but still present.[13,24,29,42,49,51]

Impacts and implications. Inevitably due to emergent use of WES/WGS, discussions of impacts of SF disclosure from WES/WGS were largely hypothetical. The most commonly cited reason against disclosure was the potential to cause anxiety or psychological harm.[24,29,34-

[36,42,44,46,47,50,51,54] This theme was widely raised in qualitative studies (Table 2): semi-structured interview and focus group designs elicited interactive and qualified opinions, providing greater insights into how SF might be construed.[30,32,39,40,42,43,47,50,51] In some of these studies, participants acknowledged becoming less inclined to desire all SF during the course of the interview or focus group.[23,39,47] Although recognized by both WES/WGS providers[34,44,50-52,54-56] and recipients,[26,39,42,47,50] potential psychological harms of SF were more frequently of concern to providers. Recipients discussed the burden of knowing, particularly about disease risk that may not affect them for some years, the potential for SF adversely to change the way they lived their lives, and incompatibility with religious beliefs.[15,30,35,40,42,47] One study found that nearly three quarters of participants factored potential distress arising from SF into their decision,[26] but for most, potential anxiety did not override their desire to receive SF.[24,34]

Stakeholders also raised concerns about overwhelming WES/WGS recipients with too much information,[55] discrimination in insurance and employment,[24,26,30,32,36,42,57] privacy,[23,27,42,45,52,55] and stigmatization.[42,48,50] WES/WGS providers, specifically, raised additional concerns: justice issues related to limited resources,[46,49,50,58] complex logistics[58,59] strains on time and funding,[46,49,58-60] lack of participant understanding,[49,61] qualification of HCPs to manage SF,[49] and that knowledge around WES/WGS is currently limited and still developing.[48,49,58] Providers were concerned that disclosure of actionable SF would warrant treatment or surveillance that may be harmful in itself, or expensive;[46] it may not always be clear how follow up might be funded, particularly in insurance-based healthcare systems.[49,58]

Literacy. Providers were often concerned that WES/WGS recipients do not always appreciate the implications of SF, and may not be adequately informed to make decisions.[46,48,49,61] WES/WGS providers who have consented patients to WES/WGS considered

that participants' lack of experience with the conditions related to SF complicates decision-making.[62] Providers felt that recipients' apparent enthusiasm for a wide range of SF—often wider than most programs currently offer—may result from incomplete understanding of the implications of SF.[48] Studies did report highly variable knowledge of WES/WGS among WES/WGS recipients, both potential and actual,[26,27,33,35,44,45,57] and providers' own understanding of SF was highly variable and sometimes insecure,[13,51,56,59,63,64] with implications for informed consent provision.

Pre-test processes. Stakeholder groups, across many studies, felt strongly that disclosure of SF should be guided by decisions made during consent.[24,34,46,60,61,65,66] To optimize informed decision-making, stakeholders in both groups felt that pre-test discussions should supplement written information.[24,50,65] Most providers felt that these discussions should include SF, while others variably included which SF would be reported, false positive/negative results, changing interpretation of variants, family, and the potential for anxiety.[55,62,63] Discussions are very context-dependent, and should be flexible and tailored to the recipient.[46,48,55,57,62] Very recent studies of HCPs' experiences with WES/WGS counseling highlighted often-unrealistic recipient expectations and the need to counteract this.[44,57,62] The length of time required to achieve informed consent was seen as burdensome for providers and recipients,[57,62] but some practitioners described increasing confidence in efficiently and effectively obtaining informed consent with experience.[46,62] Actual WES/WGS recipients, and HCPs who have consented them, acknowledged recipient difficulty in thinking about SF during consent discussions when they are preoccupied by their primary health condition.[23,62] Despite this, one qualitative study involving actual WES/WGS recipients found little support for a second consent process after the report of primary findings.[23]

Post-test processes. Members of all stakeholder groups stressed the importance of genetic counseling at disclosure of results. Face-to-face meetings with a professional who has knowledge about genetics and the implications of SF was seen as essential by WES/WGS recipients[27,32,50] and providers.[48,50,52,59] WES/WGS providers felt that disclosure discussions should take disease burden into account,[34] and be tailored to the participant, both in content and timing.[46,55,63] A quantitative study exploring counseling experience for WES/WGS found that, while both varied greatly in length, post-test discussions often lasted longer than pre-test discussions.[63] WES/WGS recipients also believed that a plan of action for clinical follow-up should be discussed at the point of disclosure,[24,30] and some envisaged a need for ongoing support.[30] Some HCPs felt they would not be able to provide psychosocial support themselves and would also require support from specialists specific to the SF disclosed.[44,64]

Family. Relatives are considered important in the management of SF, and a crucial component of informed consent and SF disclosure.[25,34,35,43,48,58] Some studies of providers highlighted difficulties with family-based recruitment and consenting,[55,57] and several studies echoed issues well described in genetics around confidentiality and the right not to know.[32,43,48,50,65,66] Some recipients cited family as motivation to receive SF, and, particularly for healthy individuals, for initial participation in WES/WGS.[25,34,40,42,47] Stakeholders across all groups are, in principle, willing to share their personal WES/WGS results.[26,27,30,32,34,35,40,45-47,55,66] However, despite wanting SF themselves, some recipients might filter SF information: sharing only actionable findings,[26,27,50,66] making decisions about impact on individual relatives[27], waiting until asked about results,[46] or being selective about which relatives to tell.[26] One study raised the potential for parents to experience guilt about the implied risk of an SF to descendants.[47]

Rights and Responsibility. The concepts of rights and responsibilities are strongly represented across the included studies. Potential WES/WGS recipients stressed the importance of autonomy—the right to choose which SF (if any) they should receive.[24,26,27,30,32,39,42,47,50] These stakeholders also expressed a strong sense of ownership, and desire for control over their genetic information.[24,26,27,30,36,42,47,49,50] This sense of proprietorship even extended to family genetic data, with some stakeholders expressing a right to be informed about genetic findings present in relatives.[26,43,48] Indeed, perceived rights to 'their' information appeared to be an important driver for potential recipients' desire for a wide range of SF: there were strong objections to paternalism, or WES/WGS providers withholding or interpreting information on recipients' behalf, in an effort to decide what is in their best interest.[13,24,50]

WGS providers agreed that participant autonomy was important, and most believed they would respect consent decisions with respect to the SF offered.[13,27,30,43,46,48,50-52,55,56,59-61,65] However, providers also perceived a strong sense of responsibility to recipients and believe that fulfilling this requires careful consideration about the utility of SF, often supporting a multi-disciplinary approach in order to reach optimally informed disclosure decisions.[43,48,59,61] Providers in one study raised concerns about determining the significance of individual variants, listing various sources of evidence (allele frequency, segregation data, previous reports, etc.) contributing to judgments, but that, ultimately, pathogenicity is often very difficult to assess.[58,61] Providers felt this uncertainty would be challenging for patients to understand.[49] Responsibility was also discussed with respect to SF management in general, with most groups agreeing that responsibility must be shared between all parties:[24,26,50,51,58,59,61,64,66] HCPs, together with WES/WGS recipients,[24,42,49,58,61] parents[26,32,36,47,50] and laboratory professionals.[51,59]

In some studies, providers' views were derived from experience with other genetic testing methods (such as prenatal or microarray-based testing) and note patients' mixed and complex reactions, unanticipated before testing, to receiving SF.[48,51] When WES/WGS recipients choose not to receive SF, some providers foresaw a possible conflict between their professional responsibility, in the duty to warn, and respecting participant autonomy.[51,59,61] Some providers considered overriding a decision not to receive SF if a clinically significant SF were found.[13,43,48,49,51,55]

Time. The idea of 'duration of responsibility' recurred in various studies and stakeholder groups. Most WES/WGS providers supported gaining consent for re-interrogation of data as new interpretations become available, and re-contact.[13,32,55,61] Potential recipients also felt that they should be re-contacted as interpretation changes or information becomes relevant, such as approaching the age at which a screening program might begin.[29,32,39,47] However, there was no consensus as to who should initiate re-contact—some felt WES/WGS recipients should share this responsibility with providers.[50,61] WES/WGS providers did consider that the duration of responsibility might differ depending on whether the program had a research or clinical focus: researchers felt that their responsibility would have to be restricted to the duration of funding,[66] and clearly communicated during the consent process.[56] Some providers had concerns that the loss of connection after the completion of a research study would complicate re-contact in a research setting.[55]

Policies and practices. Stakeholders in some studies appreciated the logistic complexity of SF management, and that it is further complicated by incomplete understanding of significance for current and/or future health.[23,48] Some raised concerns about the quality and accuracy—in terms of both analytical and clinical validity—of current sequencing technologies

and analysis,[39,49,56,58] and worried that there are currently insufficient resources to accurately to analyze the data and return it in a meaningful way.[50] Many HCPs and genomics researchers were unaware of definitive local procedures, policies or expectations around WES/WGS and SF.[48,51,54,58,64,66] WES/WGS providers discussed various options for SF management: there was support for the ACMG 'minimal gene list',[52,59,60] 'binning' or categorizing of variants,[49,61] an advisory board or multidisciplinary team,[59,61] as well as minimizing the generation of SF at the present time.[48,50,65,66] However, there was no consensus on the best approach, and other study participants voiced arguments against each of these options.[48,49,59-61] There was agreement that guidelines should be flexible, allowing for varying levels of expertise in a highly dynamic field.[43,47,48,51]

Synthesis

There is a spectrum of views about SF, ranging from generating and disclosing a wide range of SF to intentionally minimizing their occurrence. Figure 2 offers a theoretical framework that illustrates the balancing of factors that influence stakeholder preferences around SF disclosure in WES/WGS.

Potential WES/WGS recipients' views frequently fall to the less conservative end of the spectrum, favoring disclosure of a wide range of SF—often including non-medical findings as well as those that have health implications but are not medically actionable. This prompts questions about recipients' understanding of genomic complexity and difficulties distinguishing 'normal' variation from that which may be clinically significant. Preference for SF among recipients appears to be strongly associated with a sense of rights: *ownership*, and the right to their personal information, as well as *autonomy*, and the right to choose what information they receive. Potential recipients feel that they are entitled to access their genetic results if they

choose to receive them, and perceive genomics/healthcare professionals' deliberations and restriction of SF as paternalistic. This review highlights evidence from qualitative studies that recipients' stated preference for SF may be an initial response that might be subject to change with discussion and reflection on possible implications.

Providers' views are also informed by their professional responsibility to WES/WGS recipients. This sense of responsibility manifests in considered views about SF: concerned about logistics, including the analysis process and interpretation of variants, and unsure of how to handle uncertain results, providers expressed concerns about causing psychological harm by returning SF. Some studies involving HCPs contain quotes suggesting that they have personal anxieties about disclosing findings of potentially high impact[58,61] or are concerned about the range of possible SF,[64] raising a possible need for further training and support for HCPs actively disclosing SF.

Studies involving parents highlighted distinct and instructive views.[26,30,32,35,36] As with other potential recipients, parents wish to receive a wide range of SF, but demonstrate intentions to filter the information they tell their children, even when they are no longer minors. This suggests that parents balance a perceived right to their (child's) genomic information with a responsibility to protect their children from any potential harm—analogous to the balancing of benefits and harms exhibited by HCPs. Also of interest, patients with cancer diagnoses were less likely to want a wide range of SF, preferring to receive only clinically actionable findings.[27,29,35] This may stem from a contextualized understanding of the implications of genetic results for personal healthcare, based on their experience with genetic testing and illness.

Some studies postulate that greater or lesser knowledge of WES/WGS might account for the differing views. However, many of those who provided insightful responses often reported

low ‘knowledge’ of sequencing technology. These individuals, however, frequently drew on their experience with genetic disease.[27,29,42] For instance, in a qualitative study of patients with Lynch syndrome, only one participant had ever heard of WES/WGS, yet many demonstrated a very nuanced appreciation of findings from SF.[27] Across the studies, for participants who had experience with genetic illness and prior genetic counseling and testing, this informed their understanding of possible results and they expressed tolerance for uncertainty. Members of these groups—had a broad understanding of (medical) genetics, but not necessarily of sequencing technologies—were more likely to make distinctions between the kinds of SF they wished to receive. Together with genetics HCPs, WES/WGS recipients with experience of genetic testing for rare disease or cancer also appreciated that the relevance of SF is time- and circumstance-dependent. [27,29,42]

DISCUSSION

We present a systematic review and synthesis of the range of perspectives on secondary findings in WES/WGS. The review finds that there is agreement across stakeholders on the importance of patient autonomy in the management of SF. Which results should be generated and made available, however, is less clear. Participants generally support the return of ‘actionable’ findings, however definitions of ‘actionability’ varied. Stakeholders generally agreed that SF that imply life-threatening diseases for which treatment or surveillance is available were actionable and should be offered. However, study participants variously included management, lifestyle modifications and personal utility as aspects of SF ‘actionability.’ Of note, a recent systematic review found no evidence that genetic risk estimates motivate behavioral changes.[67] Nonetheless, this variability highlights the context-dependency of ‘actionability’ in SF, and poses a challenge to reaching a consensus on SF disclosure and management.

Despite differing views on what to disclose, stakeholders agreed on the concept of shared responsibility around SF disclosure. Since there is widespread agreement that SF decisions at the time of WES/WGS consent should determine which results are disclosed, it is incumbent upon providers to ensure that WES/WGS recipients are prepared for results, including implications and limitations. Education and greater understanding of the potential, and limitations, of WES/WGS and SF would support informed decision-making and narrow the gap between recipients' expectations and the current situation—where providers consider which SF are useful to generate, based on existing knowledge and resources. This remains a subject of debate,[68] and is likely to remain so for the foreseeable future as data accumulate on variant pathogenicity.

Exactly what is required to reach a sufficient level of understanding about SF is not yet clear. It appears that genetic literacy does inform stakeholder decisions and that greater understanding often results in greater circumspection about SF. This 'literacy,' however, appears to be less a technical knowledge of WES/WGS, and more a qualitative understanding of its implications and limitations. In two recent studies which explore HCP experiences consenting WES/WGS recipients, providers acknowledged a shift in the content of their pre-test discussions with experience: moving away from discussing fine details of WES/WGS to focusing on the potential results and implications.[43,62] It will be important for future studies to find ways of measuring what is important to understand in order to make informed decisions about SF.

It is worth noting the methodologies employed by the primary studies. The current perception in WES/WGS practice that recipients want a wide range of SF is informed by survey studies—presented with a tick box, recipients elect in favor of receiving all SF they are offered (and might wish for more than offered).[25,33] However, qualitative studies highlight how recipients might alter these initial thoughts later, or when they have the chance to reflect on and

discuss possible implications. If consent mirrors survey studies in the sense that unidirectional imparting of information is followed by a 'tick box' answer, individuals can be expected to elect in favor of receiving SF. The inclusion of qualitative and quantitative studies in this review allows informative comparison and suggests that for recipients to reach a holistic understanding of the implications of WES/WGS and SF, a bidirectional interaction akin to qualitative methodologies is more likely to facilitate informed decision-making. Included studies suggest that participant reflection and discussion can result in greater appreciation of the potential implications and consequences of SF; this is consistent with the fact that fewer people participate in predictive genetic testing, even for conditions for which intervention is available, than express a hypothetical intent.[69] It is likely that a one-time decision about SF may not represent WES/WGS recipients' changing views and circumstances, and more dynamic forms of consent should be considered.

Stakeholder preference is, by no means, the only factor requiring consideration in policy development around SF; further empirical research collecting data on returned SF is essential to inform stakeholder views, both on clinical utility and impacts in the broadest sense—on WES/WGS recipients, healthcare systems and society. Impacts on resources, for informed consent and genetic counseling in WES/WGS, for analysis and validation, and clinical screening and management post-disclosure, need to be assessed as part of overall healthcare priority setting.

WGS/WES initiatives are taking diverse approaches towards the issue of secondary findings in WES/WGS—this diversity, per se, represents the views of providers and the project-level discussions that have contributed to policy. It is likely that the ACMG list has influenced initiatives that have begun since its publication, with large-scale programs such as the UK

100,000 Genomes Project offering opportunistic screening of a (more limited) gene list in addition to recessive and X-linked carrier status for couples and female participants respectively. Some protocols offer an even wider range of SF,[70] while others avoid SF generation.[71] There is a possibility that WES/WGS recipients and the public will view such policy level decisions as paternalistic, and it will be important for such programs to be flexible and responsive to research findings.

Study Limitations

No studies yet report on experiences with disclosure or receipt of secondary genomic findings. Both WES/WGS recipients and providers are diverse in terms of experiences with genetic illness and testing, or professional experience with patients and/or WES/WGS. While studies of participants with direct WES/WGS experience, in particular recipients, add qualitatively to this dataset, we find no evidence from our analysis that WES/WGS experience alters the thematic areas presented here.

Discussions of return of results often include SF without referencing them explicitly. We have used broad search terms to capture variable nomenclature used by primary studies and a thorough screening process, however, due to excluding non-English studies, articles without full-text, and the variability in language, it is possible that we have missed some relevant studies.

The included studies present a predominantly white, USA perspective. Two studies that included stakeholders from other groups[40,48] presented additional data, and indicate that findings to date might not be comprehensive and representative of diverse groups.

Conclusions and Implications for Practice

In this systematic review, we have shown that the views of both WES/WGS providers and recipients with respect to returning SF exist on a spectrum. We suggest that a nuanced

understanding of the implications of WES/WGS and potential findings—rather than technical knowledge—might better inform decision-making in the management of SF. Views and preferences of providers and recipients are not fixed; they are continually informed by experience, discussion, time and circumstances. Pre-test discussions with trained practitioners are therefore essential to inform participant decisions. We recommend:

1. Further research into:
    i. the impacts of SF when returned, at the individual and family level, and on healthcare systems.
    ii. stakeholders' appreciation for the implications of WES/WGS and SF, what knowledge is required to make informed decisions about SF, and how to assess this and how it relates to decisions to receive or disclose SF.
    iii. wider perspectives on SF and WES/WGS, particularly among non-Americans and cultural and ethnic minorities, and individuals undergoing WES/WGS including parents.
2. Evidence-based training and education for HCPs providing informed consent.
3. Training and support for HCPs returning high impact SF from WES/WGS.
4. Clarifying expectations and guidelines for translational genomics research.
5. Enhancing communication and apportioning of responsibility between those involved in WES/WGS—HCPs, laboratory professionals, and WES/WGS recipients.

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COMMENT

MP serves as the chair of the Ethics Advisory Committee for the UK's 100,000 Genomes Project.

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FIGURE LEGENDS

Table 1. Characteristics of included studies

Figure 1. Study selection process

Table 2. Demographics of included studies

Figure 2. Theoretical framework illustrating factors influencing stakeholder preferences around disclosure of secondary findings in WES/WGS

Table 3. Themes discussed in each study

SUPPLEMENTARY MATERIAL AND METHODS

S1. Systematic search strategy

S3. Quality checklist for quantitative studies

S4. Quality checklist for qualitative studies

S5. Quality scores for quantitative studies

S6. Quality scores for qualitative studies

S4. Illustrative quotations

Conflict of interest: The authors declare no conflict of interest

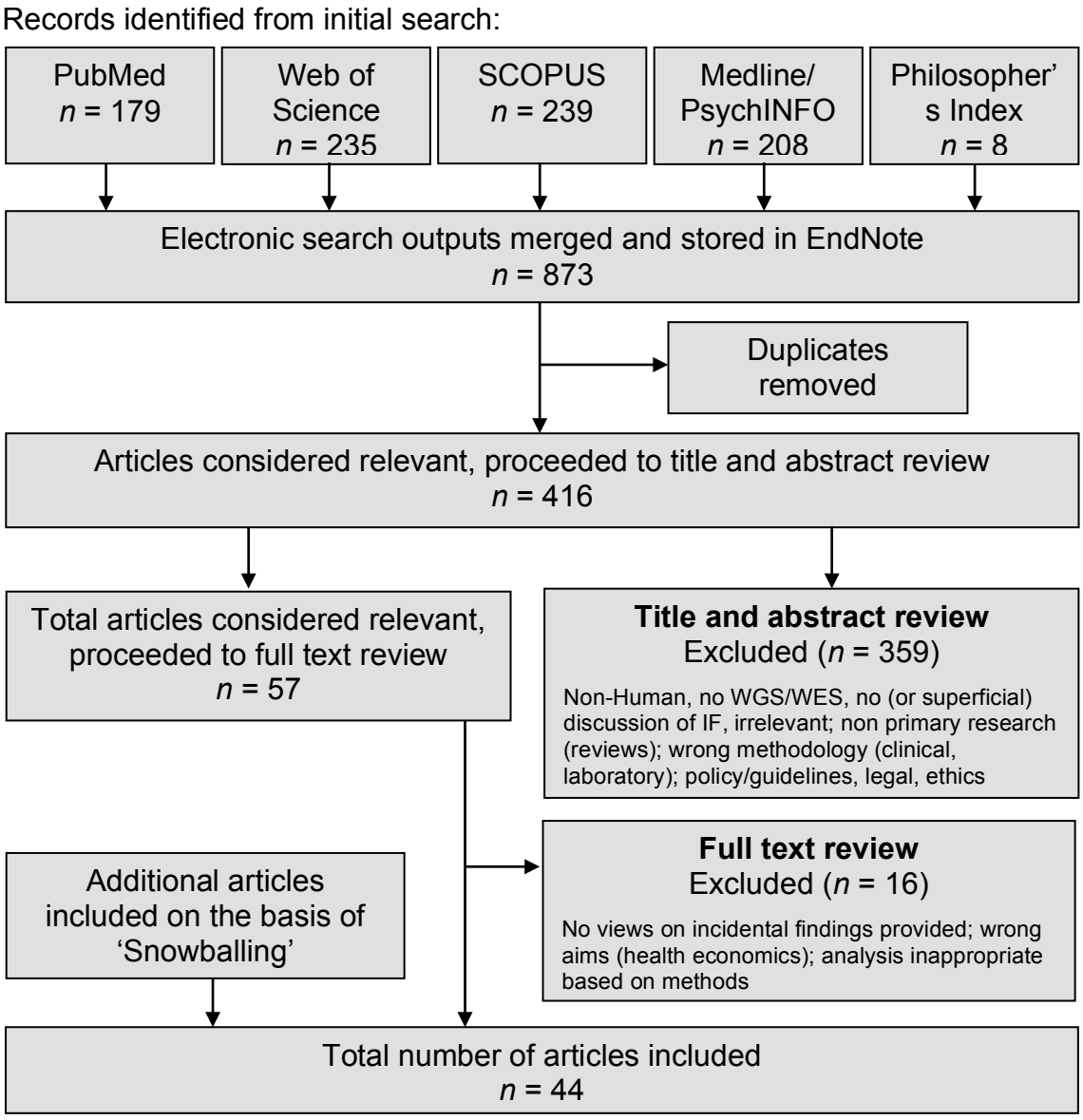

Figure 1. Study selection process

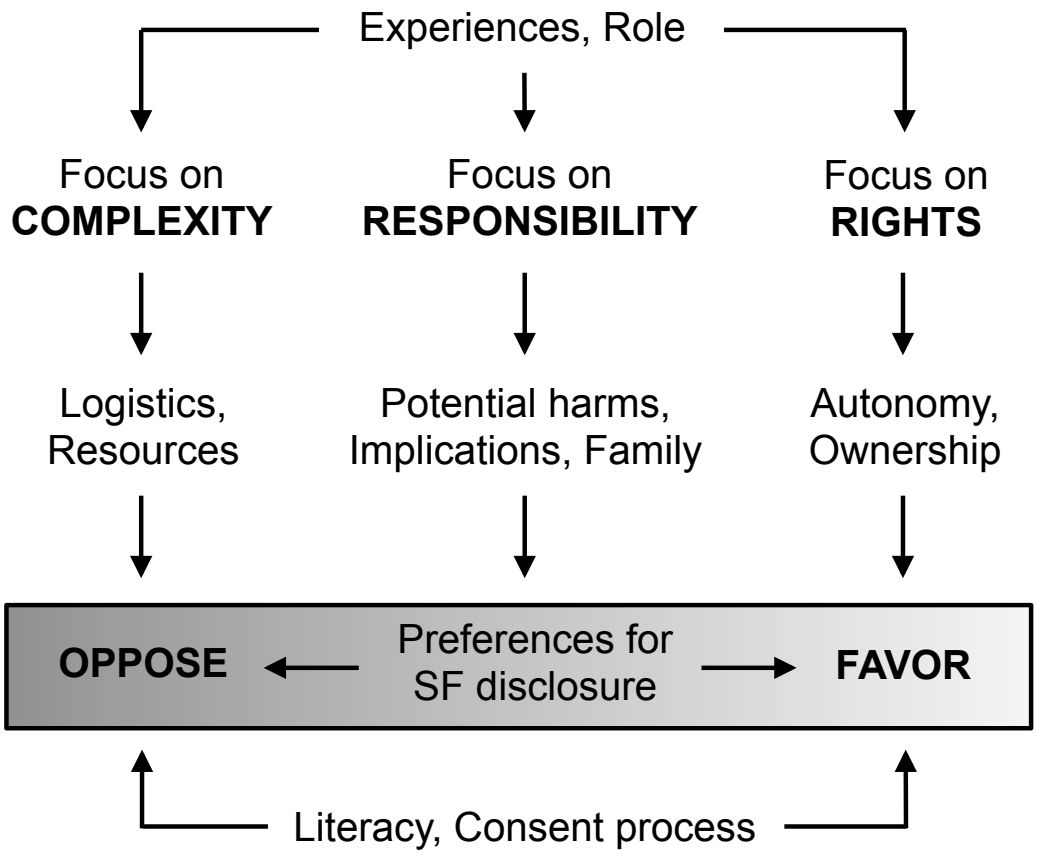

Figure 2. Theoretical framework illustrating factors influencing stakeholder preferences around disclosure of secondary findings in WES/WGS

Table 1

Table 1. Characteristics of included studies

Author/year	Country	Principal views or experiences investigated	Study Population	Participant direct experience with WGS	Domain	Design	Primary Topic
Appelbaum et al.[55]	USA	Views of informed consent process for SF	28 genomics researchers* 20 research participants	Mixed	Research	Qualitative, online survey and semi-structured interviews	WGS consent Management of SF
Arora et al.[63]	USA	Experiences providing WGS	49 genetics healthcare professionals	Yes	Clinical	Quantitative, online survey	WGS WGS consent
Barajas et al.[65]	USA	Attitudes towards opportunistic screening in pediatric genome sequencing	179 physicians (bioethicists and pediatricians)	Mixed	Clinical	Quantitative, email postal survey	Management of SF
Bergner et al.[23]	USA	Experience of the consent process in WGS	15 research participants	Yes	Research	Qualitative, Semi-structured interviews	WGS consent process
Bernhardt et al.[62]	USA	Experiences obtaining informed consent for WGS	21 genetic counselors* 8 research coordinators*	Yes	Both	Qualitative, semi-structured interviews	WGS consent process
Brandt et al.[46]	USA	Perceived importance of recommended criteria when applied to return of SF	50 genetics healthcare professionals (13 medical geneticists, 17 genetic counselors/RNs, 20 lab professionals)* 19 genomic researchers 34 IRB chairs*	Mixed	Clinical	Qualitative, Structured interviews	Management of SF
Bui et al.[45]	USA	Attitudes toward participating in and receiving results from genome sequencing	58 patients with psychiatric disorders, or unaffected family members	No	Research	Quantitative, telephone survey	Return of results
Christenhusz et al.[47]	Belgium	Views on SF and their communication	25 members of public (19 parents, 6 grandparents) 25 genetics professionals (5 laboratory staff, 7 bioinformaticians, 13 genetics students)	No	Clinical	Qualitative, Focus groups	Management of SF
Christensen et al.[64]	USA	Preparedness around providing WGS	11 primary care providers 9 cardiologists	No	Both	Qualitative, Semi-structured interviews	WGS
Clift et al.[42]	USE	Preferences towards return of SF in WGS	38 patients and parents of patients	Yes	Clinical	Qualitative, Semi-structured interviews	Management of SF

Daack-Hirsch et al.[24]	USA	Views on SF from genome sequencing in clinical and research situations	63 members of public	No	Both	Qualitative, Focus groups and interviews	Management of SF
Downing et al.[51]	USA	Preferences regarding management of SF	50 genetics healthcare professionals (13 medical geneticists, 17 genetic counselors/RNs, 20 lab professionals)*	Yes	Clinical	Qualitative, Structured telephone interviews	Management of SF
Facio et al.[25]	USA	Attitudes towards learning results from genome sequencing	311 research participants	Yes	Research	Mixed methods, in-person survey	Return of results
Fernandez et al.[66]	Canada	Attitudes towards disclosure of clinically significant research findings in context of regulatory guidance	74 genomics researchers	Yes	Research	Quantitative, postal questionnaire	Return of results Management of SF
Fernandez et al.[26]	Canada	Attitudes towards return of targeted and incidental genomic research results in setting of pediatric cancer, inherited childhood diseases.	362 parents of research participants	Yes	Research	Quantitative, postal questionnaire	Return of results Management of SF
Gourna et al.[48]	Greece	Attitudes towards clinical sequencing and return of SF	10 genetics healthcare professionals (3 clinicians, 2 bioethicists, 5 geneticists)*	Yes	Clinical	Qualitative, In-depth interviews	Management of SF
Gourna et al.[43]	Multi-national	Attitudes towards return of SF in a clinical setting	30 genetics healthcare professionals (10 clinicians, 6 genetic counselors, 8 laboratory professionals, 6 legal/ethical specialists)*	Yes	Clinical	Qualitative, In-depth interviews	Management of SF
Gray et al.[44]	USA	Views on WGS and SF	167 patients 27 oncologists	Yes	Clinical	Qualitative and quantitative, semi-structured interviews and surveys	Management of SF WGS
Grove et al.[61]	USA	Experiences surrounding SF in clinical sequencing, views on current policies/guidelines	35 members of ASHG and/or NSGC (genetics healthcare professionals)	Mixed	Clinical	Qualitative, Focus groups	Management of SF
Hitch et al.[27]	USA	Views on WGS, return of genomic results	19 patients who had undergone WES for Lynch Syndrome	Yes	Clinical	Qualitative, Semi-structured interviews	Return of results
Jelsig et al.[28]	Denmark	Attitudes towards disclosure of SF, and types of SF	127 research participants	Yes	Research	Quantitative, unclear design	Management of SF
Kaphingst et al.[29]	USA	Views on return of SF among women diagnosed with breast	60 women diagnosed with breast cancer under 40	No	Clinical	Qualitative, Semi-structured	Management of SF

		cancer	years old			interviews	
Kleiderman et al.[30]	Canada	Parental perceptions and experiences regarding the return of SF in pediatric research	15 parents of children with rare disease	No	Research	Qualitative, Focus groups and interviews	Management of SF
Klitzman et al.[49]	USA	Practices attitudes towards return of secondary findings	241 genetics researchers* 28 genomics researchers*	Mixed	Research	Multiple methods, internet survey, Semi-structured interviews	Management of SF
Klitzman et al.[58]	USA	Experiences and views concerning return of SF	28 genomics researchers*	Mixed	Research	Qualitative, Semi-structured interviews	Management of SF
Lemke et al.[31]	USA	Attitudes towards genome sequencing and secondary findings	279 genetics healthcare professionals	Mixed	Clinical	Quantitative, internet survey	Management of SF
Levenseller et al.[32]	USA	Views of for the future implementation of WES	22 genetics healthcare professionals (clinicians, bioethicists, lab directors, and genetic counselors) 20 parents 7 adolescents	Mixed	Clinical	Qualitative, Focus groups	WGS
Lohn et al.[32]	Canada	Views on the management of SF in clinical context	210 genetics healthcare professionals	Mixed	Clinical	Mixed methods, online questionnaire	Management of SF
Middleton et al.[33]	Inter-national	Attitudes towards returning SF from genome research	4961 members public, 533 genetics healthcare professionals, 843 non-genetic healthcare professionals, 607 genomics researchers	Mixed	Research	Quantitative, internet survey	Management of SF
Miller et al.[34]	Canada	Expectations and experiences of patients and providers who participate in WGS	29 patients 14 oncologists	Yes	Research	Qualitative, Semi-structured interviews	WGS Return of results
Oberg et al.[35]	USA	Challenges to informed consent in pediatric oncology research	25 parents (15 parents of children with cancer, 10 parents of children without cancer)	No	Research	Qualitative, Focus groups and semi-structured interviews	WGS consent
Rigter et al.[59]	Nether-lands	First experiences with WGS consent process	11 genetics healthcare professionals (3 clinical geneticists, 3 molecular geneticists, 2 ethicists, 1 legal expert, 1 quality manager, 2 reps from Dutch Genetic Alliance)	Yes	Clinical	Qualitative, Semi-structured interviews	WGS consent process

Sapp et al.[36]	USA	Preferences on receiving four different types of results from WES	25 parents of children with rare genetic disease	Yes	Research	Qualitative, Semi-structured interviews	Return of results
Scheuner et al.[60]	USA	Attitudes towards secondary findings in clinical genome sequencing	492 members of the ACMG (genetics professionals)	Mixed	Clinical	Quantitative, internet survey	Management of SF
Shahmirzadi et al.[37]	USA	Preferences for secondary findings from consent forms	200 patients who underwent whole exome sequencing	Yes	Clinical	Quantitative, review of consent forms	Management of SF WGS consent
Simon et al.[56]	USA	How genomic SF should be addressed in informed consent processes	34 IRB Chairs*	Mixed	Research	Qualitative, Semi-structured interviews	WGS consent process Management of SF
Smith et al.[54]	USA	How ACMG recommendations have influenced practice	46 genetic counselors	Yes	Clinical	Quantitative, internet survey	Management of SF
Strong et al.[38]	USA	Views on return of SF from WGS	258 primary care providers	No	Clinical	Quantitative, internet survey	Management of SF
Tomlinson et al.[57]	USA	Challenging experiences in obtaining informed consent for WGS	21 genetic counselors* 8 research coordinators*	Yes	Both	Qualitative, semi-structured interviews	WGS consent process
Townsend et al.[50]	Canada	Attitudes towards disclosure of SF in clinical settings	10 genetics healthcare professionals (3 physician geneticists, 3 genetic counselors, 4 laboratory geneticists), 8 parents 10 members of the public	Mixed	Clinical	Qualitative, Focus groups	Management of SF
Wynn et al.[53]	USA	How views towards SF in genomics are influenced by professional background and experience	241 genetics healthcare professionals*	Mixed	Research	Quantitative, internet survey	Management of SF
Yu et al.[40]	USA	Attitudes towards participation in WGS and return of results	41 African American members of the public	No	Research	Qualitative, Focus groups	Return of results
Yu et al.[39]	USA	Attitudes towards participation in WGS and return of results	35 Non-African American members of the public	No	Research	Qualitative, Focus groups	Return of results
Yu et al.[52]	USA	Attitudes toward return of SF from WGS	760 genetics healthcare professionals	Mixed	Clinical	Quantitative, internet survey	Management of SF

(-), unclear or unable to ascertain

(*), study population reported in multiple articles

Table 2. Demographics of included studies

Category	*n*	%
Study Type		
Quantitative	15	56.8
Qualitative	25	34.1
Mixed methods	4	9.1
Total	44	
Study Origin		
United States	32	72.7
Canada	6	13.6
Other Countries	4	9.1
Belgium	1	2.3
Denmark	1	2.3
Greece	1	2.3
Netherlands	1	2.3
Multi-national	2	4.5
Topic of investigation*		
Management of secondary findings	28	63.6
Return of results	11	25.0
WGS consent process	8	18.2
WGS, broadly	6	13.6
Participants have direct experience with WGS		
Yes	19	43.2
No	10	22.3
Mixed	15	34.1
Stakeholders represented**		
Quantitative and mixed methods studies		
Genetics health professionals	2789	25.9
Non-genetics health professionals	1128	10.5
Researchers	681	6.3
Patients	367	3.4
Research participants	858	8.0
Members of the public	4961	46.0
Total	10784	
Qualitative studies		
Genetics health professionals	204	26.2
Non-genetics health professionals	34	4.3
Researchers	55	7.0
Patients	152	19.4
Research participants	129	16.5
IRB chairs	34	4.3
Members of the public	174	22.2
Total	782	

*Total exceeds 100% as some studies were deemed to fall under two primary topics of investigation

**Parents/relatives of patients and research participants included within those groups.

Table 3. Themes discussed in each study

	Preferences, motivations	Impacts and implications	Literacy	Pre-test processes	Post-test processes	Family	Rights	Responsibility	Time	Policies and Practices
Quantitative and Mixed Methods Studies										
Arora et al.[63]			■	■	■					
Barajas et al.[65]	■			■		■	■			■
Bui et al.[45]	■		■		■	■				
Facio et al.[25]	■					■				
Fernandez et al.[66]	■			■	■	■		■	■	■
Fernandez et al.[26]	■	■	■	■	■	■	■	■	■	■
Jelsig et al.[28]	■				■					
Gray et al.[44]	■	■	■	■	■		■			
Klitzman et al.[49]	■		■		■	■	■	■		■
Lemke et al.[31]	■									
Lohn et al.[32]	■	■	■	■			■	■	■	
Middleton et al.[33]	■		■				■			■
Scheuner et al.[60]	■	■		■	■		■			■
Shahmirzadi et al.[37]	■									
Smith et al.[54]	■	■								■
Strong et al.[38]	■									
Wynn et al.[53]	■									
Yu et al.[52]	■	■			■		■	■		■
Qualitative Studies										
Appelbaum et al.[55]	■	■		■		■		■	■	■
Bergner et al.[23]	■	■		■	■					■
Bernhardt et al.[62]	■	■	■	■	■	■				
Brandt et al.[46]	■	■		■	■	■	■			■
Christenhusz et al.[47]	■	■					■	■	■	■
Christensen et al.[64]		■	■		■			■		■
Clift et al.[42]	■	■				■	■	■		
Daack-Hirsch et al.[24]	■	■	■	■	■		■	■		
Downing et al.[51]	■	■	■	■	■		■	■		■
Gourna et al.[48]	■	■	■	■	■	■	■	■		■
Gourna et al.[43]	■	■		■		■	■	■		■
Grove et al.[61]	■	■	■	■			■	■	■	■
Hitch et al.[27]	■	■	■		■	■	■	■		■
Kaphingst et al.[29]	■								■	
Kleiderman et al.[30]	■	■			■	■	■	■	■	
Klitzman et al.[58]	■	■		■				■		■
Levenseller et al.[32]	■	■			■	■	■	■	■	■
Miller et al.[34]	■	■		■	■	■				
Oberg et al.[35]	■	■	■							
Rigter et al.[59]		■	■	■	■		■	■		■
Sapp et al.[36]	■	■					■	■	■	
Simon et al.[56]		■	■	■			■	■	■	■
Tomlinson et al.[57]		■	■	■		■				

Townsend et al.[50]	■	■	■	■	■	■	■	■	■
Yu et al.[40]	■	■			■	■			
Yu et al.[39]	■	■				■	■	■	■

S1 Systematic search strategy on PubMed

01. incidental finding*
02. secondary finding*
03. additional finding*
04. incidental genetic finding*
05. 1 or 2 or 3 or 4
06. clinical sequenc*
07. genetic sequenc*
08. genomic sequenc*
09. genome sequenc*
10. exome sequenc*
11. 6 or 7 or 8 or 9 or 10
12. 5 and 11

("incidental finding*" OR "secondary finding*" OR "additional finding*" OR "incidental genetic finding*") AND ("clinical sequenc*" OR "genetic sequenc*" OR "genomic sequenc*" OR "genome sequenc*" OR "exome sequenc*")

S2 Quality Checklist for Quantitative Studies

I. Are the aims of the research clear?*
II. Is the research relevant to the synthesis topic?*
III. Was a questionnaire survey an appropriate research design to answer this question?*

*If "No" to any of I-III, paper is to be omitted from synthesis

Sampling

1. *Sampling frame:* Is the sampling frame clear, and was it sufficiently large and representative?
2. *Understanding and suitability:* Does it appear that all participants understood what was required of them, and did they attribute the same meaning to the terms in the questionnaire? Does the instrument appear to take into account the likely range of abilities of potential participants?

Data Collection

3. *Existing measures:* Did the researchers use an existing questionnaire or survey? If not, did they justify their development of a new one?
4. *Consumer views:* Were the views of consumers sought about the questionnaire?
5. *Validity:* Have the authors claimed that the instrument is valid? Is this claim justified? (i.e. Do the authors make it clear that the instrument measures what it sets out to measure?)
6. *Reliability:* Have the authors claimed that the instrument is reliable? Is this claim justified? (i.e. Do the authors make it clear that the instrument provides stable results over time and between researchers?)
7. *Pilot:* Was a pilot used on a representative sample? Was the instrument modified accordingly?

Instrument

8. *Instrument provided:* Has the questionnaire or survey been provided?
9. *Title:* Is the title of the questionnaire provided? If so, is it appropriate?
10. *Sensitivity:* Do the questions cover all relevant aspects of the problem in a non-threatening and non-directive way? (i.e. Are non-threatening questions placed at the beginning, and sensitive ones at the end?)
11. *Types of questions:* Are open-ended and closed-ended questions used appropriately?
12. *Briefness:* Is it clear that the questionnaire was kept as brief as the study allowed?
13. *Clarity:* Do the questions appear clear? (i.e. not ambiguous or overly complicated).
14. *Instructions:* Is it clear that adequate instructions were provided in the instrument? (i.e. examples answers, instructions on how to return).

Distribution, Administration and Response

15. *Method of distribution:* Is it clear how the questionnaire or survey was distributed?
16. *Method of administration:* Is it clear how the questionnaire or survey was administered?
17. *Response rate:* Is the response rate clear and reasonable?
18. *Non-participation:* Have non-responders been accounted for?

Data Analysis

19. *Description of analysis process:* Is the analysis process clearly described?
20. *Appropriateness of analysis:* Is it clear that quantitative data were subjected to statistical analysis and qualitative data to qualitative analysis (if relevant)?
21. *Accuracy measures:* Is it clear that measures were in place to maintain the accuracy of the data?
22. *Free from data dredging:* Does the study appear to be free from 'data dredging'? (i.e. No evidence that statistical analyses that were not 'hypothesis driven').

Reporting

23. *Clarity of findings:* Are the findings explicit? Have all relevant results been reported (significant and non-significant)?
24. *Data and findings consistent:* Were the findings consistent with the data provided?
25. *Appropriateness of reporting:* Are quantitative results presented as definitive (significant, non-significant)? If relevant, have qualitative results been presented with representative quotations?
26. *Relation to current practice and literature:* Have the findings been discussed in relation to current practice or research-based literature?

Checklist adapted from Boynton & Greenhalgh (2004) and Greenhalgh et al. (2005)

S3 Quality Checklist for Qualitative Studies

I. Are the aims of the research clear?*
II. Is the research relevant to the synthesis topic?*
III. Is this qualitative research (i.e. does this article report on findings from qualitative research, and did that work involve qualitative methods of data collection and analysis)? Is a qualitative method appropriate?*

*If "No" to any of I-III, paper is to be omitted from synthesis

Personal Characteristics

1. *Interviewer:* Has the interviewer/facilitator been identified?
2. *Credentials:* Have the researchers' credentials been provided?
3. *Occupation:* Have the researchers' occupations been provided?
4. *Gender:* Have the researchers' genders been provided?
5. *Experience and training:* Have the researchers stated their experience and training?

Relationship with participants

6. *Relationship established:* Is it clear whether or not a relationship was established prior to study commencement?
7. *Participant knowledge of the interviewer:* Did the participant know something about the researcher (i.e. goals, reason for research, etc.)?
8. *Interviewer characteristics:* Have characteristics of the interviewer been reported?

Theoretical framework

9. *Methodological orientation and theory:* Is it clear which methodological orientation underpinned the study (i.e. grounded theory, phenomenology, etc.)?

Participant Selection

10. *Sampling:* Is it clear how participants were selected (i.e. purposive, convenience, consecutive)?
11. *Method of approach:* Is it clear how participants were approached?
12. *Sample size:* Is the sample size given?
13. *Non-participation:* Is it clear how many and/or why some participants chose not to take part?

Setting

14. *Setting of data collection:* Is it clear where the data was collected?
15. *Presence of non-participants:* Was anyone else present besides the participant and researchers?
16. *Description of sample:* Are important characteristics of the sample discussed?

Data Collection

17. *Interview guide:* Has a topic or interview guide been provided?
18. *Repeat interviews:* Have any repeat interviews been conducted?
19. *Audio/visual recording:* Are the data recording methods clear?
20. *Field notes:* Were field notes taken?
21. *Duration:* Is the duration of the interview or focus groups clear?
22. *Data saturation:* Has the researcher discussed data saturation?
23. *Transcripts returned:* Have transcripts been returned to participants for comments/corrections?

Data Analysis

24. *Number of data coders:* Is it clear how many individuals coded the data?
25. *Description of coding tree:* Has a description of the coding tree been provided?
26. *Derivation of themes:* Is it clear how the themes were derived?
27. *Software:* Has software been used to manage the data?
28. *Participant checking:* Were results presented to participants?

Reporting

29. *Quotations presented:* Have respondent quotations been provided?
30. *Data and findings consistent:* Were the findings consistent with the data provided?
31. *Clarity of major themes:* Are the major themes presented clearly?
32. *Clarity of minor themes:* Are diverse cases, or minor themes, discussed?

COREQ Checklist adapted from Tong et al. (2007) using CASP (2013

S4 Quality assessment of quantitative and mixed methods papers

Quality Assessment Criteria		Reference																	
		63	65	45	25	66	26	28	44	49	31	13	33	60	37	54	38	53	52
Sampling	1. Sampling frame		■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■
	2. Understanding	■																	
Data Collection	3. Existing measures								■				■				■		
	4. Consumer views	■							■	■	■	■	■	■				■	■
	5. Validity				■	■	■		■		■		■						
	6. Reliability						■						■						
	7. Pilot						■		■	■	■	■	■	■				■	■
Instrument	8. Instrument provided		■	■		■	■	■	■			■	■				■	■	■
	9. Title		■	■		■	■		■				■				■		
	10. Sensitivity		■	■		■	■	■	■			■	■		n/a				■
	11. Types of questions	■	■	■	■	■	■	■	■	■	■	■	■	■	n/a	■	■	■	■
	12. Briefness		■	■		■	■	■	■		■	■	■		n/a		■	■	■
	13. Clarity		■	■		■	■	■	■		■	■	■	■	n/a		■		■
	14. Instructions		■	■		■	■	■	■			■	■		n/a		■		■
Administration	15. Distribution	■	■	■	■	■	■	■	■	■	■	■	■	■	n/a	■	■	■	■
	16. Administration	■	■	■		■	■		■	■	■	■	■	■	n/a		■	■	■
	17. Response rate		■	■		■	■	■	■	■	■	■		■		■	■	■	■
	18. Non-participation		■	■		■	■	■	■	■	■			■		■	■	■	■
Data analysis	19. Analysis process	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
	20. Appropriate analysis	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
	21. Accuracy measures																		
	22. No data dredging	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Reporting	23. Clarity of findings	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
	24. Findings consistent	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
	25. Appropriate reporting	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
	26. Practice and literature	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
	Total	12	19	19	11	20	22	17	23	15	18	19	21	16	8	12	19	17	20

(n/a), not applicable based on the research methodology employed

S5 Quality assessment of qualitative papers, as well as mixed methods papers that employed qualitative methodologies

		Reference																													
Quality Assessment Criteria		55	23	62	46	47	64	42	24	51	25	48	43	44	61	27	29	30	49	58	32	13	34	35	59	36	56	57	50	40	39
Personal characteristics	1. Interviewer					■		■	■		n/a	■	■		■	■		■				n/a		■		■			■	■	
	2. Credentials	■									n/a					■						n/a		■					■	■	
	3. Occupation			■	■			■			n/a							■				n/a									
	4. Gender										n/a											n/a									
	5. Experience										n/a						■					n/a		■							
Relationship	6. Relationship established		■								n/a											n/a				■					
	7. Participant knowledge										n/a											n/a									
	8. Characteristics			■				■			n/a											n/a									
Theory	9. Methodological orientation	■						■							■			■	■	■			■								
Participant selection	10. Sampling	■	■	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■	■	■	■	■
	11. Method of approach	■	■	■		■	■	■	■		■	■	■	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■	■
	12. Sample size	■	■	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
	13. Non-participation	■		■			■					■	■	■		■			■	■	■		■		■			■	■	■	
Setting	14. Setting	■	■	■	■			■	■	■	■			■	■	■			■	■		■	■	■	■	■	■	■	■	■	
	15. Others present					■															■								■		
	16. Sample description	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■		■	■	■		■	■
Data Collection	17. Interview guide	■			■	■	■		■	■			■	■			■	■		■		■		■		■	■	■	■		
	18. Repeat interviews							■																							
	19. Recording		■	■	■			■	■	■	n/a	■	■	■	■	■	■	■			■	n/a	■	■	■	■	■	■	■	■	■
	20. Field notes										n/a										■	n/a									
	21. Duration	■	■	■	■	■	■	■	■				■	■	■	■	■	■	■	■					■	■	■	■	■		
	22. Data saturation									■	■													■			■		■		
	23. Transcripts returned																								■						
Data Analysis	24. Number of coders	■	■	■	■	■		■	■	■	■		■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■	■	■
	25. Coding tree					■														■				■		■					
	26. Derivation of themes			■			■	■			■	■			■		■		■	■	■			■					■	■	■
	27. Software	■	■	■	■	■	■	■	■	■	■	■	■	■	■		■	■		■	■			■	■	■	■	■	■	■	■
	28. Participant checking																														
Reporting	29. Quotations	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
	30. Findings consistent	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
	31. Major themes	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
	32. Minor themes	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
	Total	16	14	17	14	15	13	17	15	13	13	12	15	16	16	15	15	15	14	17	14	11	12	19	14	17	15	15	19	16	12

(n/a), not applicable based on the research methodology employed

S6 Illustrative quotations from the primary studies for each theme

Preferences for secondary findings

- *Affected adult research participant:* "And then as far as discovering other things, I mean, if there's something else going on, I'd like to know now so that if there's treatment or things that I'm doing that I need to stop doing, I'd definitely like to know that."[23]
- *Member of the public:* "It's just all so arbitrary, it's so, so, unbelievably person-dependent and situation-dependent and disease-dependent too, I don't know."[47]
- *Medical genetics specialist:* "If it's not going to impact [the patient], and they didn't ask about it, I probably wouldn't share it"[46]
- *Medical genetics specialist:* "Personal utility has never been the purpose of medicine…I think the idea of actionability, as the idea to change treatment, the medical actionability, is the way to go on with this. This is the way we think in medicine."[43]

Impacts and implications

- *Medical genetics specialist:* "[W]hen these incidental findings come up in a prenatal setting, the anxiety, the turmoil, that I see out of this is tremendous…"[51]
- *Adolescent patient:* "I'd rather be surprised than know it's coming, because that's worse, to me…because if I can't cure it, the anxiety of when it will come would make me sick."[32]
- *Affected adult research participant:* "Like these crazy movies they're based off of that information gets to the wrong people and somehow they do crazy stuff, but I don't see that happening."[23]
- *Researcher:* "The number of potential IFs is essentially infinite. The amount of overhead for identifying and reporting incidental clinical findings would destroy the research enterprise in genetics."[49]

Literacy

- *Researcher:* "Most people don't think hard about the implications. The casual comment "I want everything" is usually not so reflective of what people want once they've really thought and been educated about it."[49]
- *Patient with lynch syndrome:* "Unless you might have something that will impact your health in the future, I don't know if it's good or useful for just anybody to get to see their whole genetic makeup."[27]
- *Genetic counselor:* "I don't think of incidental findings as things like variants of uncertain significance, but that's a different issue altogether, but they sort of get jumbled in my head."[51]

Pre-test processes

- *Genetics healthcare professional:* "I think one of the most important factors is the pre-test consent. Patients have the right to choose if they would like to obtain information about themselves above and beyond information about the pertinent clinical question.

The types of results should be explained to the patient who can then decide what they want or don't want to know."[13]

- *Genetic counselor:* "I mean, you'd have to have a 10-hour counseling session to talk about all of the things you might find."[51]
- *Researcher:* "The problem with the consent process is whether to be as detailed as you want. I'm always very fearful that a subject is just going to turn off and just sign, or just say, 'Forget it,' because we come up with these well-intentioned, but terribly long consent documents."[55]

Post-test processes

- *Researcher:* "You have to tune into the person, what their needs are, and their level of understanding. I tend to err on the side of trying to give them a lesson in what the genetics of this are, and walk them through this as systematically and slowly as I can…It depends a lot on the perception you have of how much the patient is able to understand and wants to understand. We don't handle it exactly the same way every time."[55]
- *Medical genetics specialist:* "I think [it depends on] what the patient is ready to hear…if you've got eight things to discuss you don't have to throw all eight at a patient or a family immediately in the first 10 min of a counseling session and then clean up the mess. I think you can deal with it over time…To prioritize…in a manner that allows the patient or the family to adapt…gain knowledge and then be able to handle something new."[46]
- *Parent of affected child:* "Absolutely verbal. […] It would almost seem uncaring just to receive it on a piece of paper."[30]
- *Parent of child subjected to WGS:* "Sometimes you need these things translated…My concern would be... are all GPs…able to interpret the results of the testing?"[50]

Family

- *Member of the public:* "... the biggest thing... is... physicians having a problem: 'Do I disclose to other family members?' That's where the confidentiality issues arise. If you find something that's definitely inheritable... do you tell everyone? ... What if they don't want to know?"[50]
- *Member of the public:* "I may not want this information but the generations that come after me, Insha'Allah, God willing, could come back and access it."[40]
- *Patient with lynch syndrome:* "I'm someone who can really handle information and not get too freaked out by it, but it's a fine delicate balance of like telling someone if they have something that's completely unrelated to, you know, what I've been going through. I think I'd ask them if they want to know and I would really think about it and probably get the opinion of a genetic counselor."[27]

Rights and Responsibility

- *Pediatric genetics healthcare professional:* "This is the nanny state rearing her goat head again! No one should be forced to undergo testing and receive information that they don't want."[65]

- *Patient eligible for WGS:* “I also heard that someone makes that decision on the basis of ethics and that’s what made me think: Well, aren’t we man enough to decide for ourselves to decide what [unsolicited findings] we think is responsible to hear or not.”[59]
- *Genetic counselor:* "It is absolutely their right to choose…but I think it would be really difficult if we knew something that was medically important, possibly treatable…"[51]
- *Researcher:* "Incidental findings with clinical utility, e.g., BRCA1 and BRCA2, should be disclosed, period, and the participant should be told to expect a call if those show up. They should not be deciding [for themselves and relatives] to ignore it."[49]
- *Genetics healthcare professional:* “I think if you tried to be paternalistic and dictate there were things that we shouldn’t tell them then you may get a lot of push back from patient advocacy groups.”[50]
- *Patient:* “I’m wondering why is it even an issue of the doctor having a say? I mean it’s your genome. It’s your body...”[50]
- *Genetics healthcare professional:* “It is not our role to withhold information but instead to make this information accessible and understandable to our patients. Once reported, it becomes part of those patients’ medical records and therefore information they are entitled to have.”[13]

Time

- *Genetic counselor:* “What I need today from my genome sequencing isn’t what I’m gonna need 5 years from now. And I think about the preventive you know timeline that we look at in the doctor’s office every time you go to see your OB-GYN. When I’m 20-25, I need to have my cholesterol screened once every 5 years. I need to have, so having something like that in the whole genome, what do I need to unlock and what do I need to, do I need to find out about this now? […] What do I want, so some concept like that I think needs to be flushed out.”[61]
- *Patient with breast cancer:* “They still don’t fully understand it, but at some point, hopefully they will. … They would be able to go back and say okay, now we have something we can use with this information.”[29]
- *Genetics healthcare professional:* “You can certainly put the onus on the patient... but I don’t think that you can put the onus on the lab or the physician’s office to retroactively review all of their cases where ‘X’ variant was found because now there is this new information on ‘X’ variant.”[50]

Policies and practices

- *Researcher:* “I would never return, even think of returning something that’s coming out of next-gen[eration] sequencing right now.”[49]
- *IRB Chair:* “The dilemma, of course, is whatever incidental finding has been discovered…it’s never clear how accurate that information is, how correct it is, and whether it is meaningful to the subject.”[56]
- *Clinical molecular geneticist:* “[An advisory board] is of course something that in the long run will be unmanageable. At a certain point in time, we will have to report our

findings within two weeks and if every incidental finding has to pass a committee, that will never work."[59]