Eur J Med Genet **56**(10): 529-540. DOI: 10.1016/j.ejmg.2013.08.006

Disclosing Incidental Findings in Genetics Contexts: A Review of the Empirical Ethical Research

Short running title: Review on the disclosure of incidental findings

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Abstract

The disclosure of incidental findings, also called unsolicited findings, unexpected results, and secondary variants, is increasingly recognised as an issue in clinical and research genetics contexts. The rise of next generation sequencing methods has only intensified the issue, increasing the likelihood of incidental findings appearing. This review focuses on empirical research on the ethical issues involved. Electronic databases were searched for articles covering quantitative and qualitative research on the ethical issues involved in the disclosure of incidental findings in clinical and research genetics contexts. 16 articles were ultimately accepted for review. Data was extracted and synthesised on the factors that should be taken into account during the decision-making process surrounding the disclosure of an incidental finding in a genetics context. These factors include the possibility of disclosure, various practical and technical factors, and various ethical factors. We suggest the development of a decision-making tree, involving an exploration of the practical and ethical concerns raised by the studies. This is in our view the best way of handling the wide variety of both possible incidental findings and parties interested in the disclosure of incidental findings.

Keywords

disclosure; incidental findings; ethics; genetics

Introduction

Incidental findings (IFs) have been defined in research contexts as findings having potential health or reproductive importance for an individual research participant, discovered in the course of conducting research but beyond the aims of the study. [1] The term itself is somewhat contested. [2] Some authors prefer alternative terms such as unsought for findings, unsolicited findings, and off-target results. [3-5] They have been reported most frequently in neuroimaging, oncology and genetics contexts. [1] However, despite a multitude of case reports, opinion pieces and general articles attesting to the widespread and frequent appearance of IFs in all sorts of research and clinical contexts, there is very little public guidance available at a government, professional or academic level, and what is available is inconsistent. [6-8] There have been several systematic reviews published in recent years on IFs arising in imaging contexts. [9-11] However, the focus of these systematic reviews is generally the frequency of IFs; how to handle IFs, and ethical explorations or justifications of particular ways of handling IFs, are touched upon in the discussion section of each article but are not the aim of any of the reviews.

It is unclear whether IFs can be said to exist in clinical contexts, because it can be argued that all results, whether beyond the aims of the study or not, are actually included in the aim of clinical care and are thus not "incidental". [12, 13] Nonetheless, making a distinction between what is the target of a clinical test or procedure and what is more "off-target" can be useful when developing consent procedures that sufficiently inform patients and/or guardians about both types of results, [4] as well as useful when devising follow-up procedures and formulating professional obligations. Similarly, it is helpful in research contexts to make a distinction between research results and IFs, because there are key differences between the two, related to whether the finding falls inside or outside the domain

or expertise of the researcher, and whether the obligations for the researcher are clear or ambiguous. [13] The present review involved a search for literature on what are commonly accepted to be IFs: findings that fall outside the aim of the study, and/or are unanticipated, and/or are not the specific focus or target of the particular research or clinical query.

In a previous article, we performed a systematic literature review of the ethical reasons presented in the argument-based literature for and against the disclosure of IFs arising in clinical and research genetics contexts. [2] The present review also focuses on the disclosure of IFs arising in genetics settings, but this time based on the empirical research that has been done thus far. As next generation sequencing technologies move from research to clinical contexts and become increasingly widespread, the huge amounts of data of widely varying significance that they produce make IFs a growing issue. [14-16] We continue to use the term "incidental findings" because it is the keyword most commonly used to describe the phenomenon, although we do have reservations about this term. [17]

Methods

Search methods

Articles were sought that fulfilled four criteria: empirical research, in research or clinical genetics settings, ethically focused, and related to the disclosure of IFs. Various keywords were entered in several electronic databases for each of the four categories (Figure 1). Articles published before 2001, the year in which the initial sequencing and analysis of the human genome was completed, were excluded, as the completion of the human genome project marked a crucial turning-point in the practice of genetics. [18] The Pubmed searches were saved and weekly electronic updates requested until June 2013.

Articles were excluded if IFs or similar concepts were mentioned only in passing, only research results were considered, there was no empirical research conducted, or there was no reflection on ethical issues. By the latter we understand explicit treatment of established ethical principles and concepts, [19, 20] or reflection on the values and attitudes motivating actions and opinions. [21] Articles on screening, biobanking and direct-to-consumer genetic testing were also excluded, as these raise additional public policy and social issues, and have been covered in several recent reviews. [22-24] Finally, the references of all the articles included up to this point for review were scanned, and citation searches were run on all the included articles in Web of Science.

Data extraction and synthesis

The resulting articles utilised a range of quantitative and qualitative methods, covering a range of clinical and research genetics contexts and targeting a number of different publics. Due to this considerable heterogeneity, it was inappropriate to pool the data in a meta-analysis. The data are instead presented in summary form (Table 1). A quality appraisal of the articles was conducted using the quality assessment tool (Qual Syst) developed by Kmet *et al*. (Supplementary Tables S1 and S2). [25] Given the relatively limited number of articles eligible for review, the cut-off point chosen for article inclusion was what Kmet *et al*. designate as the relatively liberal quality score of 55%. A thematic analysis of the articles revealed that the single issue running through all articles was the factors relevant during the decision-making process surrounding the disclosure of an IF. Data extraction was subsequently conducted to identify these factors.

Results

The electronic database searches resulted in 126 possible articles for review (excluding duplicates; Figure 1). There were 16 articles ultimately accepted for review. [26-41] Snowballing resulted in no additional articles. A high proportion of articles were included that were published in the last two years, [26-29, 31-35, 39-41]confirming the relevancy of the topic.

A range of characteristics of the reviewed articles are listed in Table 1, for comparison. All received a quality score of more than 55% (Supplementary Tables S1 and S2), and thus were included for subsequent review. Our analysis disregards the fundamental methodological differences between quantitative and qualitative research, as well as the specific research question of each article, in favour of an extraction and synthesis of themes. It was not the intention of the current paper to determine what the most important or most cited themes are.

Thematic analysis led to the discovery of a single issue recurring in all articles: what factors should be taken into account in genetics contexts during the decision-making process surrounding the disclosure of an IF? We have taken this issue to structure the data extraction and synthesis of this review. The study-specific results, related to which precise factors such as gender or lifestyle influence disclosure preferences and decisions, have little or no value in guiding clinical or research practice, and are not dealt with here.

The possibility of disclosure

The first important factor to be taken into account during the decision-making process is whether disclosure is in fact a possibility. That is, are the medical professionals (be they clinicians or researchers) and the potential recipients of the IF open to the possibility of disclosure, or have they already indicated that disclosure is not an option? [26, 35, 38, 39] The

reviewed articles dealing with medical professionals indicate a general consensus that clinically significant IFs should be returned. [26, 28, 29, 33-35, 37, 40, 41] This in many ways matches the reported general desire of non-professionals to receive clinically significant IFs. [28, 30, 32, 36, 40] However, the potential presence of a sizeable minority wishing to exert their right not to know, alongside the varying impact of certain demographic and health factors on disclosure preferences, indicate the need for a thorough procedure to determine potential recipients' wishes. [36] Such pre-test discussions are useful to avoid "surprises", incorporate patients and parents in decision-making, and make it clear to patients if geneticists have intentionally limited the possibility of IFs. [28, 40] Consent forms should be specific enough to help when later making a disclosure decision, according to genetics researchers, [33] while also leaving room for the possibility of participant disclosure preferences changing over time, according to IRB chairs. [39]

Practical and technical factors

Another group of factors cited in the reviewed articles as relevant in the decision-making process are practical and technical factors. This group of factors can be further divided into three subgroups. A first subgroup involves questions around the clinical utility of the finding, including the seriousness, urgency, treatability (dependent also on cost, impact and availability), impact on the quality of life, probability and disease context of the finding. [26, 28-30, 32-38, 40, 41] A second subgroup involves scientific factors: whether the finding has been replicated and by an independent research group; the robustness and quality of the finding (e.g. whether the finding comes from a known coding region); how expected or "incidental" the finding is; and the extent and complexity of the information provided by the IF. [27-29, 33, 35, 37-40] A third subgroup involves communication factors: who should disclose and to whom; the capacity of the team to handle complex and uncertain data, explain

the IF sensitively and comprehensively, and provide medical advice; the capacity of the patient or research participant to understand the finding; complex family dynamics, including how to respect the growing maturity of children; and the possibility or necessity to consult colleagues and the institutional review board about the finding. [26-28, 31-33, 37, 40]

Ethical factors

A final group of relevant factors dealt with in the reviewed literature are ethical factors. By this we understand established ethical principles and concepts, [19, 20] as well as the values and attitudes motivating actions and opinions. [21] This group of ethical factors can be further categorised into subgroups. It should be noted that several of the subgroups overlap.

Several articles mention the ideals of maximising benefits and minimising harms. [26, 27, 32, 37, 40] Beneficence and non-maleficence were cited by genetic researchers in one interview study as motivations for both the disclosure and non-disclosure of IFs. [37] The specific harms of disclosing IFs mentioned in the reviewed literature include possible risks to privacy and confidentiality, insurance and employment discrimination, and various psychological harms such as fear, anxiety and confusion. [26, 27, 31, 32, 40] There was also the concern on the part of researchers that research participants may not have the support or resources necessary to understand the risks of IFs and take appropriate follow-up steps. [37] It is noteworthy that while the lay people in one study responded to the possibility of harms stemming from IFs by starting to speak about their autonomy, health care professionals in the same study responded by continuing to speak in terms of beneficence and non-maleficence. [40]

Respect for autonomy and choice is an additional relevant ethical factor, though sometimes contentious. [26, 27, 35, 37, 39, 40] The lay groups in a focus group study on

clinical whole genome sequencing (WGS) spoke of the ideal of autonomous decision-making, and considered respect for autonomy and choice to be the basis for disclosure, not the clinical relevance of the IF as decided by a professional. [40] Some IRB chairs involved in an interview study argued that respect for the autonomy of research participants is a higher value than beneficence, distinguishing between research and clinical care. [39] In their view, the informed consent process presents the perfect opportunity to respect potential participants' autonomy. In contrast, some clinical genetics professionals surveyed set actionability and definite beneficence above patient choice. [35] Similarly, some genetic specialists in an interview study reported that they would find it very difficult if patients had opted out of disclosure and an IF was discovered with known clinical significance. [27] Some IRB chairs in a related interview study stated that they would give more weight to a medical opinion favouring disclosure or nondisclosure on grounds of the participant's beneficence than the participant's own preferences. [41] One IRB chair involved in another interview study conducted by the same group spoke not just of the recipient's right to know and respect for their autonomy but of their "need to know" in certain life-threatening or life-changing cases. [26] Some researchers in another interview study were also of the opinion that participants should have access to clinically relevant information and the choice to learn this information; the authors of the study note that the "right not to know" was not always acknowledged by interviewees. [37]

The principle of justice featured in focus group discussions with health care professionals and lay people on the equitable use of limited resources. [40] Moreover, the ideas of property and ownership in terms of IFs specifically or the genetic sequence as a whole fall under the concept of justice, as well as being related to respect for individual autonomy. [40] At the same time, it was acknowledged that the inherited nature of genetic information complicates questions of ownership.

The theme of duties and responsibilities is a further subdivision of ethical factors relevant in the decision-making process. [26, 31, 32, 37, 40, 41] Medical genetic specialists, genomic researchers, and IRB chairs involved in an interview study spoke of their obligation to respect the wishes of the participant or patient to receive an IF. [26] Primary care professionals in focus groups spoke of their duty to disclose IFs, especially when treatable conditions were involved, while geneticists in the same study were more hesitant when applying the specific term "duty" to themselves. [31] Lay people in a related study agreed that health care professionals have an obligation to disclose IFs. [32] Some researchers spoke of the responsibility that they feel towards those participating in their research projects. [37] Some set this against the context of research, and said they feel a certain sense of responsibility because of the trust that participants commit to the researchers and their expertise; others simply set it against the context of the normal give-and-take of human relationships. The need to balance the duties of researchers to individual participants and society was acknowledged. [37] Some genomic researchers involved in an interview study stressed the purpose of research, to generate knowledge, as a reason not to disclose IFs. [41] Mention was also made in one reviewed study of the responsibility that patients have, especially in terms of keeping up with new implications of their genetic data due to advances in genetic knowledge. [40] Health care professionals in this study related the idea of patient responsibility with the practical challenges facing professionals, while for the lay participants it was more an idea of mutual patient-clinician responsibility, linked to the idea of patient choice.

Finally, the presence of a minor has an impact on the decision-making process. [28, 29, 34, 35, 40] Two surveys of clinical genetics specialists uncovered increased reluctance to disclose IFs when minors were involved compared to the situation involving adults. [29, 35] This reluctance was shared by professional stakeholders involved in an interview and focus

group study on paediatric genomic research and clinical practice, and was especially related to IFs involving reduced penetrance, variable expressivity, delayed onset, or the absence of any available treatment. [28] In contrast, public stakeholders involved in the same study were willing to accept any ambiguity surrounding IFs as simply part of the ambiguousness of life. Their desire to receive IF information was motivated by a wish to be prepared. It was their view that parents should decide if, when and how IFs are shared with their children, although medical professionals should act as a backup to ensure that children do receive certain types of IFs once they reach a certain age. [28] A survey of clinical genetics professionals revealed that the presence of a minor had a variable influence on the decision-making process, depending on the actionability and the time of onset of the IF. [34] Focus groups involving health care professionals and lay people related the presence of a minor to broader issues of inheritance and ownership of genetic information. [40]

Discussion

Any attempts to pull together the results of the reviewed studies need to be done carefully, because of both the high degree of heterogeneity in terms of study aims and target populations and the relatively limited number of studies that have been published to date. An additional challenge encountered while conducting this review is that while a range of search terms in a number of electronic databases were trialled, complemented by the snowballing method, there is no guarantee that all relevant literature was identified simply because of the heterogeneity of terms and keywords used in empirical bioethics publications. [42] We nonetheless consider this review to be an important exercise in order to gain an overview of the empirical ethical research that has been conducted up until now on the disclosure of IFs. Given what some anticipate as a huge increase in expected IFs as whole exome and genome

sequencing methods make the transition from research to clinical contexts, [14, 43] an overview of the issue is urgently needed. In addition, the fact that 75% of the articles reviewed in the present paper have been published in the last two years emphasises that there is currently a large amount of empirical research being done on this topic.

As already stated, the general view of medical professionals that clinically significant IFs be returned, [26, 28, 29, 33-35, 37, 40, 41] in many ways matches the general desire of non-professionals to receive clinically significant IFs. [28, 30, 32, 36, 40] The study-specific results, related to which precise factors influence disclosure preferences and decisions, have little or no value in guiding clinical practice, and have been largely disregarded in the present review. However, this is not intended to be the take-home message of the studies. Their point is more that we should be aware of the gap that exists between agreeing in general to a policy of disclosure and the specifics of each IF. These specifics include the specific context of the IF itself (including its clinical validity and utility, whether it is serious or not, how far it lies from the original aim of the genetic test), the context of the medical professional making the discovery (including their particular medical field, their ethical culture, their professional support network), and the context of the subject in whom the IF is discovered (including whether a minor is involved). With respect to the specific context of the IF itself, the development of categories of IFs accompanied by recommendations for how to deal with each category is urgently needed. Such discussions have already begun. [43, 44] This is a first step in answering the call of several of the studies for clear guidance on the disclosure of IFs. [27, 29, 31, 37, 40] However, with respect to the people involved in the IF – the patient or research participant whose IF it is and the person who has made the finding – it is not categories or checklists that will help but counselling and other forms of dialogue. This issue was raised in some of the reviewed articles, which advocate a thorough pre-test discussion between medical professional and subject, [31, 32, 35, 36, 39, 40] and the need for more educational resources.

[31, 37] The discrepancy between a given IF on the one hand and the subject's reasons for desiring disclosure and the context in which disclosure will occur on the other hand is starkly apparent in recent literature on why genetic testing for BRCA and Huntington's mutations is pursued. [45, 46] We suggest that a sort of "decision-making tree" may be a useful and user-friendly tool in coping with disclosure decisions in the clinic and research.

A decision-making tree would need to start by separating technical or practical concerns and ethical concerns, [47] as we have done in structuring the results of the reviewed literature. The initial question of whether disclosure is an option or not can be incorporated into the group of practical and technical concerns. Green *et al*. make a distinction in the discussion of their study results between clinical judgments regarding the clinical validity or utility of the IF and ethical judgments based on whether adults or minors are involved. [29] At the beginning of a new field it is prudent to begin by exploring the extent of pragmatic concerns and clinical judgments that are possible. However, it is time to move on in the context of IFs arising in clinical and research genetics. For instance, it has now been well established that new genetic sequencing techniques such as WGS raise ethical issues because of the huge complexity and ambiguity of the data generated, [14] and this was confirmed as a concern in several of the studies reviewed above. [28, 31, 33, 37, 39, 40] Now is the time to move on to reflections about why exactly this raises ethical issues; for example, how exactly does complex and ambiguous information challenge the abilities of medical professionals to maximise benefits and minimise harms (thus furthering beneficence and maleficence), or challenge the abilities of the subjects of genetic tests to act autonomously?

We envisage a decision-making tree with two major branches, one for technical or pragmatic concerns and the other for ethical concerns (Figure 2). The technical factors should be dealt with first when deciding to disclose an IF, because it can be argued that they form the basis of being able to address ethical factors such as maximising benefits and minimising

harms. In other words, it makes little sense to reflect on the ethical factors at play in the disclosure of a particular IF if the very clinical utility and validity of the finding are in doubt and the communication process will be problematic.

Figure 2 thus sets technical factors before ethical factors in the decision-making process. We have arranged the three types of technical factors that came out of the reviewed literature according to what to us appears a logical order: clinical utility, scientific factors, and communication factors. A ranking of ethical values was apparent in some of the studies when considering the relative value of respect for autonomy. [35, 39, 40] Thorough ethical reflection is needed to consider how to rank ethical concepts and even whether ranking is an ethically sound idea. Given that ethical concepts are necessarily lived out in particular cultural and professional contexts, as Green *et al*., among others, illustrate, [29] it may prove difficult to devise a ranking of concepts that can be universally applied. The implementation of a decision-making tree may help avoid an *a priori* ranking of ethical concepts, by allowing different concepts to take on different weights depending on the specific context. What is certain is the importance of considering multiple factors in any single decision-making process. [26]

Figure 2 is not yet a "decision-making tree" as it does not include any decisions, as such. It is a schematic representation based on the results of the present review of the factors that would need to be considered when disclosing an IF in genetics contexts. The branches and twigs on the current schematic can be added to in more detail based on the more thorough results listed above. There is room to add to the tree on the basis of other reviews. [2, 48] Our intention is not that such a tree be used by individual researchers or clinicians, but that it be a tool for use in team discussions on the disclosure of IFs. The importance of team discussions was highlighted in several of the reviewed articles. [29, 33, 37]

An example will help to illustrate how such a decision-making schematic might be used. Imagine that a clinical geneticist incidentally discovers a mutant *BRCA1* gene during WGS involving a four year old girl. Following the first branch of the tree, the geneticist and their team should first consider the clinical utility of this IF and various scientific and communication factors. This is a serious IF, related to breast and ovarian cancer. A carrier of a *BRCA1* mutation has an average risk by age 70 years for breast cancer of 65% and for ovarian cancer of 39%.[49] The information is currently not very urgent for the four year old girl, but it will be of later personal importance. It could be very relevant information now for the girl's mother, aunts and grandmothers. In terms of treatability, there are early screening and prevention options, such as prophylactic mastectomy. The disease context is cancer, and it may also be relevant to consider the initial reason for carrying out WGS (the "intentionality" of the finding) and whether there is a family history of breast or ovarian cancer. Various scientific factors should be checked, such as the replication, robustness, quality, and extent of the finding, as should the communication factors listed in the results section above such as who should be the recipient of this IF.

Moving to the second branch of the decision-making schematic, the following reflections come to the surface. In terms of maximising benefits, early screening resulting from the disclosure of this IF can lead to early detection, and prophylactic surgery can remove the risk almost completely. This should be weighed against minimising the possible harms of unnecessary anxiety for the child, possible over-treatment, and stigmatisation. In the context of justice, it can be asked whether it is just to devote resources to the validation, communication, and follow-up of this particular IF instead of to other health issues. It is also unclear who exactly the "owner" of this IF is, the little girl herself or maybe all her female relations (giving them the chance to also get tested). When a child is involved, it is not always obvious whose autonomous choice should be respected: that of the child, now, or of the child

once she reaches majority, or of the parents, her legal guardians, who can then choose how they want to handle the IF. Duty and responsibility issues include balancing the provision of clinical care to the family against a just distribution of finite resources. They also involve asking questions like: who is the clinical geneticist responsible for in this case? The child, the child and her immediate family, or the broader family too? Reversing the question means considering how the parents can best fulfil their responsibilities as parents and family members in this case. Is it possible that they could learn of this IF through other means, thus respecting the right of their child not to know? Finally, the age and possibly the gender of the child is a factor; additional questions would be raised if she were 14 years old, or a 17 year old boy.

The problem of IFs has been identified as "one of the greatest impediments" to the immediate introduction of whole genome and exome sequencing in clinical medicine. [29] Given that medical professionals are generally in favour of disclosing clinically relevant IFs, and patients and research participants are generally in favour of receiving clinically relevant IFs, efforts should now be spent on ironing out the details, investigating when exceptions may arise and what to do when they do arise.

Acknowledgements

This work was supported by FWO Flanders, project number G029107 and G.0594.09. K Devriendt is senior clinical investigator of the FWO-Vlaanderen. We sincerely thank Ms Lieslot Mahieu for the tree in Figure 2. We also wish to thank the anonymous reviewers for their valuable comments and suggestions.

Conflict of interest.

The authors declare no conflict of interest.

Figure titles and legends

Figure 1: Results of the electronic database searches. The search string used was: (qualitative research OR cross-sectional studies OR questionnaires OR health surveys OR cohort studies OR focus groups OR peer review) AND genetics AND ethics AND (incidental findings OR truth disclosure OR disclosure)

Figure 2: Decision-making schematic for use in the disclosure of an incidental finding in genetics contexts. This tree is based on the results of the present review, and is intended for use in team discussions on the disclosure of incidental findings. The following factors should be considered when coming to a decision about disclosing a particular incidental finding: 1) Technical factors: a) clinical utility: seriousness; urgency; treatability; impact on quality of life; probability; disease context; b) scientific factors: the replication, robustness and quality, intentionality, and extent and complexity of the incidental finding; c) communication factors: who should disclose and to whom, communication capacity of the team, comprehension capacity of the recipients, family dynamics; possible/necessary consultation of colleagues/IRB. 2) Ethical factors: a) maximise benefits; b) minimise harms; c) justice issues: just distribution/utilisation, and property, ownership, and inheritance issues; d) respect for autonomy; e) duties/responsibilities: towards individuals and society, and from the viewpoint of the medical professional and the recipient; f) presence of minors.

Tables

Table 1: Summary of a range of the characteristics of the 16 reviewed articles. The final column lists the factors mentioned by each article relevant in the decision-making process surrounding the disclosure of an incidental finding (IF).

Author/s (Year)	Country & setting	Study population	Aim	Research design	Sample size and response rate (RR)	Summary	Factors relevant to incidental findings decision-making
Brandt, Shinkunas, Hillis, Daack-Hirsch, Driessnack, Downing, Liu, Shah, Williams, Simon (2013)	USA; medical genetics	professionals (medical genetic specialists, genomic researchers, IRB chairs)	to examine how a range of professionals perceive the relative importance of recommended criteria when applied to genetic/genomic IFs	qualitative - telephone interviews	103 professionals obtained through stratified purposive sampling (RR n/a)	professionals' perspectives on nine selected criteria proposed in the literature regarding the importance of IF disclosure	the IF points to a life-threatening condition (and this may influence responses to other criteria); individuals indicate in writing they wanted to be informed of IFs; there is a treatment (dependent on cost, impact and availability); quality of life will most probably be affected. Discussion around disclosing an IF regarding a reproductive risk for the individual's offspring. Less important criteria: analytic validity, high penetrance, association with early onset and relative risk more than 2.0. Also: do a risk-benefit assessment; consider the nature of the IF; consider the unique recipient of the IF

Downing, Williams, Daack-Hirsch, Driessnack, Simon (2013)	USA; clinical genetics	genetics specialists (medical geneticists, laboratory professionals, genetic counsellors, genetics nurses)	to examine the perspectives of clinical genetics specialists regarding the management of IFs	qualitative - telephone interviews	50 genetics specialists obtained through purposive sampling (RR n/a)	key issues highlighted include inconsistent definitions of IFs, when and how to inform patients, minimising psychological harm, and having flexible disclosure guidelines	how certain the significance of the IF is; possible psychological harm (anxiety, turmoil); patients' difficulty in understanding the IF
Driessnack, Daack-Hirsch, Downing, Hanish, Shah, Alasagheirin, Simon, Williams (2013)	USA; paediatric genomic research and clinical practice	broad cross-section of professional and public stakeholders in paediatric genomic research and clinical practice	to capture the unique issues and challenges surrounding the discovery and disclosure of incidental genomic findings when children are involved	qualitative - interviews and focus groups	103 professionals, 63 members of the public, obtained through purposeful, stratified sampling (RR n/a)	one overarching theme: "it's hard for us; it's hard for them"; distinctions separating professionals from lay groups clustered around three subquestions: what to disclose, who gets the information, and what happens later?	professionals: the complex nature of interpreting IFs eg the accuracy in predicting associated phenotypes; easier decision when the IF is clear and life-threatening or actionable, more difficult if untreatable or adult-onset; complex family dynamics and growing maturity of the child relevant in communication; consider carefully the possible impact on the child of disclosure, including for their later reproductive choices. Lay groups: ambiguity is a fact of life, so not repelled by the ambiguity of IFs; desire to receive information so as to be prepared; parents should decide if, when and how IFs are shared with their children

Green, Berg, Berry, Biesecker, Dimmock, Evans, Grody, Hegde, Kalia, Korf, Krantz, McGuire, Miller, Murray, Nussbaum, Plon, Rehm, Jacob (2012)	USA; clinical genetics	clinical geneticists and/or molecular medicine specialists	to explore specific conditions and types of genetic variants that specialists in genetics recommend should be returned as IFs in clinical sequencing	quantitative - survey	16; RR not reported	considerable concordance on what to return (80% agreement for 65% of the conditions), discordance on what factors influence decision-making; a small panel of experts will not be able to agree on what to return	treatability or prevention possibilities; quality of the finding; presence of a minor
Haga, O'Daniel, Tindall, Lipkus, Agans (2011)	USA; clinical pharmaco-genetic testing	public	to explore public attitudes regarding pharmacogenetic (PGx) testing and the role ancillary information might play in decisions to undergo such tests	quantitative - explorative, random-digit-dial telephone survey	n=1 139 (RR=42%)	the potential of ancillary information does not negatively impact public interest in PGx testing, possibly even the opposite; interest in learning ancillary information is well-aligned with the public's desire to be informed about potential benefits and risks prior to testing	interest of potential recipients in incidental findings; seriousness and treatability of the finding; disease context
Haga, Tindall, O'Daniel (2012a)	USA; clinical pharmaco-genetic testing	health care professionals (primary care professionals [PCPs] and geneticists)	to assess health care professionals' attitudes on pharmacogenetic (PGx) testing, ancillary disease risk information and related clinical issues	qualitative - focus groups with questions and a hypothetical vignette	21 health care professionals, 3 focus groups	positive interest in PGx testing, though less for PCPs because of various concerns; many PCPs feel an obligation to disclose, geneticists not because of the complexity of results. Authors recommend more educational resources, access to genetic specialists, and clear clinical guidelines about the use of PGx testing	potential psychological risks (fear); duty to disclose; communication challenges

Haga, Tindall, O'Daniel (2012b)	USA; clinical pharmaco-genetic testing	general public from Durham, NC	to gain a better understanding of the views of the general public on pharmacogenetic (PGx) testing, ancillary disease risk information and related clinical issues	qualitative - focus groups with questions and a hypothetical vignette	45 individuals, 4 focus groups	enthusiastic about PGx testing; most participants agreed that doctors are obliged to disclose ancillary risk information, though some were then hesitant about actually learning it; concerns of privacy, confidentiality, and psychological harms from ancillary information; implications for physicians	duty to disclose; actionability of the finding; possible harms (anxiety, psychological harm, insurance discrimination); question of who discloses
Hayeems, Miller, Li, Bytautas (2011)	Canada/inter-national; genetic research	cystic fibrosis and autism genetic researchers	to better understand a range of factors that might influence how researchers establish clinical significance and reportability	quantitative - quasi-experimental; international cross-sectional survey	2187 possible authors, 877 eligible participants, 785 eligible surveys, RR 44%	80% agree in principle that clinically significant findings be disclosed, but specific judgements varied based on scientific factors, capacity of the team to explain the results, and type of research ethics guidance; the type of researcher, their primary role and their beliefs about a general reporting obligation also had an impact; results call into question the assumption that everyone will return the same results	replication, robustness, and intentionality of the finding; extent of the information; specificity of the informed consent; clinical utility; disease context; consultation of colleagues and IRB

Lemke, Bick, Dimmock, Simpson, Veith (2012)	USA; clinical genetics	clinical genetics professionals	to investigate the views of clinical genetics professionals on WGS and IFs when it involves themselves, their children, and adults and children in a clinical care setting	quantitative - survey	279 clinical genetics professionals; approximately 90% uptake rate	participants' views were strongly dependent on clinical actionability and the presence of a minor: the vast majority agreed that they were interested in knowing about clinically actionable IFs in themselves (96%) and their child (99%), and that these types of IFs should be disclosed in adult (96%) and minor (98%) patients; percentages dropped to around 70% for an adult-onset clinically actionable disease and a childhood-onset, non-clinically actionable disease, and dropped even further for an adult-onset non-clinically actionable condition	clinical actionability of the IF; presence of a minor
Lohn, Adam, Birch, Townsend, Friedman (2013)	Canada; clinical whole genome sequencing (WGS)	geneticists and genetic counsellors	to investigate the views of geneticists and genetic counsellors in Canada on the disclosure of IFs arising from clinical sequencing investigations	quantitative - online questionnaire	210 clinical genetics professionals; RR 42%	geneticists and genetic counsellors largely in agreement that actionable IFs should be readily disclosed to patients while other IFs should not be readily disclosed; pre-test informed consent process emphasised	nature of the finding (ranging from a serious and treatable condition to an IF with social implications eg non-paternity); presence of a minor; test accuracy; evidence indicating pathogenicity; what was agreed upon if there was a pre-test counselling session

Matsui, Lie, Kita, Ueshima (2008)	Japan; genetic research	research participants	to investigate the actual preferences of donors [of genetic samples] with regard to receiving individual results; to explore the factors related to their decision	quantitative - prospective population-based genetic epidemiologic study; two item questionnaire	1845 (99.4%) for question 1, 1767 (95.2%) for question 2, 1758 (94.7%) answered both questions	most participants want to be recontacted and want reports of IFs; some sociodemographic associations	interest of potential recipients in incidental findings; disease context
Meacham, Starks, Burke, Edwards (2010)	USA; genetic research	researchers	to better understand researchers' problem-solving strategies, reasoning processes, and motivations for dealing with the challenge of IFs	qualitative - semi-structured telephone interviews, with 5 hypothetical vignettes	60 researchers from Washington State and Oregon, of a possible 125 (RR=48%); 44 responded to the return of unexpected results vignette	primary question is how to disclose, related to 3 potentially conflicting duties: information quality, participant welfare, adherence to rules. Also important: involving others and practical considerations	clinical utility; quality and replication of the finding; maximise benefits and minimise harms (reasons for and against disclosure) and the support and resources necessary to do this; duties of researchers; communication issues; right to know
Ries, LeGrandeur, Caulfield (2010)	Europe/North America (Canada, Denmark, England, France, the Netherlands, USA); genetic research - birth cohort studies	investigators involved in 6 birth cohort studies	to examine how a sample of birth cohort studies in North America and Europe has handled certain key ELS issues (recruitment, nature of consent sought, confidentiality and sample/data protection measures, handling sensitive information, disclosure of results, withdrawal)	qualitative - semi-structured telephone interviews	lead investigators from 6 birth cohort studies, out of a possible 14 contacted (RR=43%)	not all studies tell participants about how sensitive information will be handled; studies vary on whether results of more routine tests and measures will be returned, nothing of unknown clinical significance returned	possibility of disclosure; clinical utility; scientific validity; actionability

Simon, Williams, Shinkunas, Brandt, Daack-Hirsch, Driessnack (2011)	USA; research genome-wide association studies (GWAS)	institutional review board (IRB) chairs at centres conducting GWAS	an exploratory descriptive study to gain a preliminary understanding of emerging IRB perspectives and practices in relation to addressing genomic incidental findings (GIFs) in informed consent processes	qualitative - semi-structured interviews	34 chairs; RR n/a ("purposive sample" and interviews continued until saturation was reached)	most chairs reported no knowledge of local IRB requirements regarding GIFs and informed consent, though several had experience with IFs; several suggestions made about how to improve consent processes; concerns regarding participant disclosure preferences changing over time, inherent limitations in determining the scope and accuracy of claims about GIFs, and making consent processes longer and more complex	the autonomy of research participants and their right to change their mind regarding disclosure preferences should be respected in the informed consent process
Townsend, Adam, Birch, Lohn, Rousseau, Friedman (2012)	Canada; clinical whole genome sequencing (WGS)	genetics health-care professionals, the general public, and parents whose children have experienced genetic testing	to explore and compare practical and ethical issues concerning disclosure of IFs in clinical settings from the perspective of some stakeholders	qualitative - focus groups	10 genetics health care professionals (RR=10/24); 8 parents (RR=8/(25*2?)); 10 lay people (RR n/a)	5 dominant themes emerged: pre-test discussions (important, but disagreement on whether IFs could be categorised or not), patient choice, patient responsibility (for following up future developments, because of limited clinical resources), communicating IFs (with sensitivity and comprehensively), impact and implications of IFs (anxiety, discrimination, wider family)	pre-test discussion and other communication issues; clinical relevance including seriousness, urgency, treatability, probability; also clinical relevance from the patient's viewpoint; justice; property and ownership, also in terms of the broader family; respect for autonomous choice; minimise potential harms (confusion, anxiety, possible discrimination); responsibilities of health care professionals and patients; presence of a minor

Williams, Daack-Hirsch, Driessnack, Downing, Shinkunas, Brandt, Simon (2012)	USA; research genome-wide association studies (GWAS)	genomic researchers and institutional review board (IRB) chairs at centres conducting GWAS	to examine researcher and IRB chair perspectives on genomic incidental findings (GIFs)	qualitative - semi-structured telephone interviews	19 genomic researchers and 34 IRB chairs from 42 institutions; RR n/a ("purposive sample" and interviews continued until saturation was reached)	researchers favoured policies offering a case-by-case determination of GIF disclosure after discovery; IRB chairs favoured policies determining procedures for GIF disclosure prior to approval of the research	researchers: generally not in favour of disclosure as not coinciding with the purpose of research, to generate knowledge; GIFs with clear or probable medical significance should be disclosed, while GIFs of uncertain significance were seen as a difficult issue. IRB chairs: beneficence and minimising harm could be reasons to override a stated desire (not) to know

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Supplementary tables

Supplementary table S1: Quality of the quantitative studies identified for review, assessed according to the quality assessment tool (Qual Syst) developed by Kmet *et al*. (2004). Articles with a quality score higher than 55% were included for subsequent analysis.

Supplementary table S2: Quality of the qualitative studies identified for review, assessed according to the quality assessment tool (Qual Syst) developed by Kmet *et al*. (2004). Articles with a quality score higher than 55% were included for subsequent analysis.