

# Management of Incidental Findings in Clinical Genomic Sequencing Studies

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**Whole-genome approaches, which are replacing targeted tests in research and clinical practice, increase the chances of ‘incidental findings’ (IFs) – that is, those unrelated to the reason for the test. IFs raise several challenging questions, such as are researchers obliged to disclose IFs, and does this change if the researcher is also a clinician? How can the clinical significance of IFs be determined, and what significance level should determine disclosure? Could family members be tested to help to clarify significance, and if so, how? What should happen if adult-onset risks are found in children or prenatally? No consensus currently exists about disclosing IFs from research, or about how participants can be helped to make decisions about and give consent (not) to receive them. We recommend that as more research studies that**

**use genome-wide tests are launched, longitudinal empirical work be conducted to explore participants’ experiences and inform best practice for consent and, where relevant, feedback.**

## Introduction

Over the past few years, sequencing a whole genome has become quicker and has fallen in cost from US\$10 million to several thousands. As a result, genome-wide approaches, such as chromosomal microarray analysis (CMA) and whole-exome sequencing or whole-genome sequencing (WES/WGS), are replacing the previously routine techniques of karyotyping and genetic tests targeted to specific genes. This transition is taking place in both research and clinical practice, and in the adult, childhood and prenatal settings. These new techniques have a greater potential to uncover a genetic basis for complex and heterogeneous conditions such as intellectual disability, when the genetic contribution to the disease is unclear (Yang *et al.*, 2014).

Sequencing a whole genome or exome can be akin to administering a whole-body MRI scan to find a cause for a person’s backache. As with any new technique that is more sensitive than the one it replaces, more findings outside the target area – some easy to interpret, others not – will be made. Findings unrelated to the question that initiated the test are often called ‘incidental findings’ (IF). Early empirical data show that the clinical incidence of

## Advanced article

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Figure 1 Alternative terms to IFs.

IFs ranges between 1% and 7% (Schuol *et al.*, 2015), depending on whether the test used is CMA, WES or WGS.

We have argued elsewhere that IF is not always the best term, especially as researchers/clinicians sometimes actively search for ‘additional findings’. However, alternative terms – shown in **Figure 1** – each have limitations (Shkedi-Rafid *et al.*, 2014). We use the term IF because it has gained the most traction in current debates. The term IF has also been used in, for example, neuroimaging and biochemistry contexts. However, while most imaging or biochemical IFs are informative of the current health of the patient, genomic IFs can predict future risks and have relevance to family members and the tested person. For example, Nguyen *et al.* (2015) reported five cases of copy number variants detected by CMA in the dystrophin gene in girls referred in for developmental delay. This finding had immediate relevance to male family members, in whom early diagnosis can improve clinical management. Carrier females can face some symptoms and reproductive implications, but these would be relevant to them only in adulthood.

In this article, we will explore some of the many questions raised by IFs in genomic studies, such as should IFs be disclosed and if so, when? How can tested individuals be best prepared for the possibility of IFs? Should IFs for adult-onset risks discovered in children or foetuses be disclosed? Should information about undisclosed IFs be stored and for how long? We will focus mainly on the research setting in this paper, but as described in the next section, the boundary between research and clinical practice can be blurry.

## Distinguishing Research from Clinical Practice

Broadly speaking, although they inevitably overlap, the obligations of researchers towards participants differ from those of clinicians to patients. The aim of research is usually to obtain generalisable knowledge relevant to a particular group, which may not bring any personal benefits to individual participants. Researchers’ first and foremost obligation is to ensure that participants are making a free and informed choice to participate in the research. On the other hand, clinicians have a duty of care to their patients and are required to consider their interests at all

times, based on the best evidence available to them (Crawford *et al.*, 2013).

Despite these different emphases in respective roles, some have questioned whether researchers have an ethical duty to provide individual results, including IFs, to research participants, on the basis that they have a right to know or a right to access their individual data and that the information might be clinically useful to them. Debates about the disclosure of results to research participants have shifted over time, from the mid-1990s when most institutional review boards required researchers to make clear to participants that they would not receive individual results, to the past decade where several working groups have recommended ‘research results that are valid, medically important and actionable’ (Jarvik *et al.*, 2014) be returned, as long as participants have consented to receive them, the participants are identifiable and there is funding for the return (Jarvik *et al.*, 2014).

Such recommendations can be hard to implement in practice. For one, and as we explain later, IFs can be explained in only a broad and general sense at the outset of a research project, making ‘fully informed’ consent unlikely. Secondly, research funding for individualised approaches, which can be expensive, is often insufficient and not the aim of the research. Thirdly, research protocols may not have the same quality assurance procedures that clinical diagnostic practice has, meaning results found in a research setting have to be validated in a clinically accredited laboratory, and therefore transfer from research to clinical practice is required (Hallowell *et al.*, 2015; Kleiderman *et al.*, 2015). Researchers themselves have expressed a preference for any such disclosure to come from genetic healthcare professionals, but research teams infrequently include clinicians qualified to disclose IFs (Gourna *et al.*, 2015). A survey of 234 US genetics researchers showed 93.7% thought it would be a burden on researchers if the disclosure of some IFs was compulsory (Klitzman *et al.*, 2013). In another study (Kleiderman *et al.*, 2015), researchers thought participants should ideally have access to their information, but research projects lacked the necessary infrastructure to confirm IFs or explain them to participants.

A related question that some have explored is whether researchers should actively search for a list of ‘additional findings’. Although US guidelines state that researchers do not have a duty to do so (Weiner, 2014), this is a narrow legal position, which may not reflect what a researcher might feel a responsibility to do, or what they might be found wanting for not doing. Indeed, Gliwa and Berkman (2013) have suggested that researchers might be morally obliged to search if it could prevent serious disease or death, if participants have no other way of obtaining the information, and if the search would not burden the researcher. While the authors conclude that genomic research projects might fulfil these criteria in the future, researchers do not currently perceive such an obligation. One survey, which sought the views of over 5000 people – researchers, clinicians, patients and the public – showed only 30.7% expected researchers to actively search for additional findings (Middleton *et al.*, 2015). In another survey of 74 genomic researchers and clinician-researchers, results similarly showed that most (63%) strongly disagreed/disagreed with the idea that they have a responsibility to look for findings – although most (68%) also strongly agreed/agreed that they would have an obligation to

report an IF if found (Fernandez *et al.*, 2013). For those who indicated that researchers had a responsibility to offer disclosure, they primarily saw the duration of this responsibility as linked to the project period (51%) or by ongoing access to a database holding the results (22%), and less so as an indefinite and ongoing responsibility (14%). There was no consensus about returning variants of unknown significance (VOUS) to participants: researchers said they would want to work with clinicians to make decisions about such findings. Notably, in this study, researchers who also had a clinical role were significantly more likely than researchers to report a feeling of responsibility to examine the data for additional findings. Indeed, clinician-researchers can perceive particularly complex responsibilities to report findings that could help participants (Kleiderman *et al.*, 2015).

The research-clinical practice boundary is not always clear, especially as participation to research studies is sometimes offered to patients in the clinic, and some studies promise clinical feedback. One example is the United Kingdom's 100 000 Genomes Project, where WGS is offered to National Health Service patients with a rare disease or cancer. In the former group, testing is offered in 'trios', that is, to two family members, usually parents, as well as the patient, because doing so helps to interpret the sequence and the pathogenicity of certain findings (see [genomicsengland.co.uk](http://genomicsengland.co.uk)). Testing is done within a health setting primarily to make a clinical diagnosis, but patients/parents can participate only if they also consent to future research on their sequence data. Participants can choose to have their genomes searched for a list of additional findings that are treatable or preventable. The way this model works in practice will likely evolve over the next few years. It will be important to consider issues such as good practice in consent and whether participants understand if and what results they will receive – particularly as previous research shows that participants sometimes do not (Hallowell *et al.*, 2015).

## Difficulties Assessing Clinical Utility and Validity

Clinical utility and clinical validity (see Glossary) are two considerations used to determine whether IFs should be disclosed and whether additional findings should be actively looked for in research studies, including the 100 000 genomes project. However, it can be difficult to determine whether a finding is 'actionable' and thus which findings have clinical utility, and experts disagree over what 'counts' as an action (Gourna *et al.*, 2015). Individual participants' contexts can have an influence, for example, a Huntington disease IF might not be considered actionable unless the participant is pregnant or planning a pregnancy, and even then, some might disagree that preventing the birth of a child falls into the category of a clinical action. Clinical validity is not always straightforward either, firstly because benign changes are sometimes mislabelled as pathogenic, and some IFs will be false positives (Bell *et al.*, 2011). Secondly, different bioinformatic pipelines can assign different clinical significances to the same variant (O'Rawe *et al.*, 2013). Thirdly, the penetrance of the IF might be variable, for example if the associated phenotype ranges from normal to severe. Some variants –VOUS– might

never have been encountered before or described in the literature, making it difficult to assess their clinical significance without further research (Shkedi-Rafid *et al.*, 2014). Understanding the clinical validity and prevalence of such variants might be possible as WES/WGS is used more frequently and there is an accumulation of more population data. The scale of the data required to make interpretations is so great, however, that it often will take years to accumulate.

Overall, findings will not often have clear-cut clinical significance when they are discovered, and as we have argued elsewhere, such findings can be more accurately conceptualised as 'potential IFs', the significance of which might become clear only after large-scale population studies (Crawford *et al.*, 2013). This is yet another reason researchers do not disclose them. In the short term, to clarify clinical significance of an IF, researchers could use genomic data from other family members who are involved in the research. If the variant is carried by all affected and no unaffected individuals, it might explain the phenotype. If the variant is carried by both affected and unaffected individuals, it could be that it is not fully penetrant, or that it does not explain the phenotype. Familial testing would be possible if the research used trios, as with the 100 000 genomes project. Alternatively, researchers could report the findings to the participant's clinician, who could attempt to engage family members. This process entails additional time and financial costs for the researcher and emotional costs and uncertainty for the participants and their family. Genetic testing research suggests that patients can find it difficult to contact family members about a genetic risk (McClellan *et al.*, 2013; **See also: [Disclosing Genetic Information to Family Members: The Role of Empirical Ethics; Genetic Information Access, a Legal Perspective: A Duty to Know or a Right Not to Know, and a Duty or Option to Warn?](#)**). In the genomics context, communication might be especially difficult because of the complexity and uncertainty of the information. Nevertheless, research from the United States and Canada suggests people would share genomic information (Fernandez *et al.*, 2014; Hitch *et al.*, 2014), and what's more, perceive a right to be informed about gene discoveries in a sibling, even in the absence of effective treatment or prevention (Fernandez *et al.*, 2013; Kleiderman *et al.*, 2014). Family communication might be addressed in the consent process of the research study or clinical encounter, but even so, can be difficult for participants to envisage at that stage.

## Existing Guidelines about Disclosing IFs from Research

Reviews of international norms, legislation, guidelines and decisions made by institutional review boards have revealed that IF disclosure is infrequently addressed specifically in these documents. There is a general lack of consensus on this issue (Knoppers *et al.*, 2015; Simon *et al.*, 2012; Zawati Van Ness and Knoppers, 2011). Terms and concepts are not defined in the same way and there is no harmonised vision of what should be returned, when, how and by whom (Kleiderman *et al.*, 2015). Recent guidelines from the United States (Weiner, 2014) therefore urge researchers to design protocols that include specific sections on

**Table 1** Policies from recent and current research projects

Study name	IF policy
The Liver Disease Project, Canada	Samples are stored in a 'Liver Disease Biobank'. Researchers offer the participants IFs that 'clearly indicate a significant health problem that can be treated or prevented' and ask participants to provide the name of a health professional who can pass this information on during the consent process (Thorogood <i>et al.</i> , 2014)
Deciphering Developmental Disorders (DDD), United Kingdom	Researchers do not report any IFs discovered in the course of their analyses. Patient information sheets clearly state that IFs will not be reported back (Middleton <i>et al.</i> , 2013)
Prenatal Assessment of Genomes and Exomes (PAGE), United Kingdom	Researchers have so far not reported IFs and VOUS discovered in the course of their analyses (Drury, 2015)
100 000 Genomes Project, United Kingdom	Parents can consent to have their child's and their own genomes interrogated for additional findings (currently cancer and cardiac predispositions with risk-reducing/treatment options). The children can consent for themselves if they are 16 years old or over and/or deemed to have capacity to consent. For parents, additional findings can also include carrier testing for risks of diseases that could affect future children. Some carrier results will be revealed as 'carrier couple' results, that is, revealed if both parents are carriers, as only this combination can result in an affected future child (see <a href="http://genomicsengland.co.uk">genomicsengland.co.uk</a> )

reporting IFs, to allow participants to choose which to receive and to discuss these decisions with participants. **Table 1** contains a summary of policies adopted by a selection of large-scale research studies regarding the disclosure of IFs additional findings. In general, the decision to disclose has depended on the seriousness and clinical utility of the IF.

## Specific Issues with Paediatric Genomic Tests

Guidelines and legislation in many countries suggest that testing children for adult-onset conditions should generally be deferred until they can decide for themselves whether they want to be tested (Botkin *et al.*, 2015). However, with IFs, the question is not about whether to test the child, but whether to reveal information already found, raising questions about whether adult-onset risks should be disclosed in these cases.

Knoppers *et al.* (2014) argue that in the research setting, such IFs generally should not be reported, but they acknowledge that sometimes the child could benefit from disclosure of even an adult-onset risk, as serious, highly penetrant and actionable IFs could be clinically relevant for parents. They argue that the child's best interest should be a guiding principle in decisions to disclose IFs and their possible disclosure 'should be discussed during the informed consent process.' They also argue that difficult cases where the child and family could directly benefit from being informed about an IF should be assessed on a case-by-case basis.

Nondisclosure raises questions of whether researchers should contact the child when the finding becomes relevant, about how information should be stored in the meantime and whether stored information should be reanalysed for more findings that are pertinent. There is no European consensus about how data

from laboratory tests should be stored and IT systems are not sufficiently geared to ensure that delayed disclosure can be rigorously implemented. State-run healthcare programmes in Europe mean that liaison between research and clinical services might provide a solution to disclosure that US-based recommendations do not hint at. Another option is to use filters to remove information about adult-onset risks from children's sequence data, although this would mean that information with possible immediate benefit for relatives would not be revealed.

## Specific Issues with Prenatal Genomic Tests

The issues around adult-onset IFs in children are also relevant to the prenatal setting, with the obvious difference that women/couples might terminate pregnancies based on the identification of future risks. Decisions are particularly difficult when the clinical significance of an IF is not clear. Much of the discussion about how to maximise the benefit of prenatal CMA while addressing concerns about IFs has come from a clinical context. There, some laboratories use lower resolutions to look at the fetal genome, so only large deletions and duplications, or small deletions and duplications known to cause specific syndromes, are identified (Ahn *et al.*, 2014). This reduces the risk of ambiguous or uninterpretable findings, but also the diagnostic potential of the test. Other laboratories use higher resolutions, prioritising detection of all deletions and duplications and relying on interpretation of pathogenicity (Gardiner *et al.*, 2015). Others have argued that the fetal genome should be interrogated for a list of additional actionable findings (Alamillo *et al.*, 2015). Questions about the best option are likely to become more pertinent as noninvasive prenatal testing is used more widely.



## Research Participants' Disclosure Preferences

Several research studies have explored participants' preferences about IFs. Of these, few have explored attitudes to receiving adult-onset risks identified in pregnancy. Walser *et al.* (2015) showed that clinicians found it important to disclose all types of results from prenatal CMA, including risks for adult-onset conditions (treatable and nontreatable), carrier status and VOUS. Srebniak *et al.* (2011) showed that about half of the parents undergoing prenatal CMA testing wanted to be informed of adult-onset conditions found incidentally. Kalynchuk *et al.* (2015) and Walser *et al.* (2015) showed that such parents found it important to know about adult-onset conditions, both treatable and nontreatable.

Many more studies internationally have explored hypothetical views of patients affected by hereditary cancers (Hitch *et al.*, 2014) and parents of children affected by developmental delay (Christenhusz *et al.*, 2014). Findings show that, although they are particularly keen to learn about 'actionable' IFs, they generally want to receive all IFs from a genomic test – even if there is no available intervention. Real-life choices made by 200 adults in a study by Shahmirzadi *et al.* (2014), who used a 'menu' approach to the consent process, reflected these preferences: only six chose to blind some results, most commonly recessive carrier status results, which would not affect them but their future children if the other parent was also a carrier.

Overall, participants think that having a choice about which findings to receive is important, and this is for several reasons. Participants think that knowledge is empowering and that results not clinically actionable could have 'personal utility' (i.e. be actionable in ways such as preparing financially for early-onset disease). Moreover, where the tested person is a child, parents worry that the information might be lost if not disclosed right away and that they have a duty to their child to seek information about their health. By contrast, those reluctant to learn about IFs, and even those who want to know, acknowledge that IFs could be overwhelming, cause anxiety or distress or lead to discrimination from insurance companies (Christenhusz *et al.*, 2014; Hitch *et al.*, 2014; Kaphingst *et al.*, 2015; Kalynchuk *et al.*, 2015; Regier *et al.*, 2015). **See also: Incidental Findings in Genetic Research and Genetic Testing**

A limitation of the existing research on participants' preferences is that it has been cross-sectional rather than longitudinal. Therefore only initial preferences rather than those based on considered decisions have been sought, and satisfaction or regret at decisions has not been explored. Moreover, most research has been hypothetical: for example, in Christenhusz *et al.* (2014), none of the parents had actually received IFs. Hypothetical views can lack context and be poor predictors of actual decisions. Many of the published questionnaire studies have also elicited rights-based views, linked to a sense that researchers/clinicians should not withhold information about people and that people have a 'right to know' information about themselves. These views may change as it becomes clearer that such IFs will not often stare the researcher/clinician in the face, but will instead require an active search of the data and analysis of any information found

(Middleton *et al.*, 2015). Longitudinal research about real-life decisions is thus warranted.

## Consent for Genomic Research

The problem of hypothetical decision making is also relevant to the way participants make decisions about IFs in real-life research settings. That is, at the time of consent and decision making, participants may not have had the opportunity to think about their choices or their implications (Klitzman *et al.*, 2013), throwing into question how meaningful and informed their decisions can be. Consent for IFs can be a time-consuming and challenging process, because the huge range of potential findings is difficult or impossible to explain and discuss in a specific and detailed way (Bertier *et al.*, 2015) – especially for researchers who do not have clinical expertise (Applebaum *et al.*, 2014).

A few studies shed light on these difficulties. Bergner *et al.* (2014) found that 20 participants who in the previous nine months had consented to a study about WES/WGS for Mendelian disorders were able to describe the concept of IFs and give examples, but they also found the consent process taxing. Furthermore, and as in other studies (Reiff *et al.*, 2014; Rigger *et al.*, 2014), participants did not take much time to think about their decisions, because they perceived the likelihood of an IF to be small and because they were mainly concerned about getting a diagnosis. One study (Tabor *et al.*, 2012) showed that families found it hard to understand WGS and anticipate their feelings about receiving IFs even after 2–3 h of discussion and reading supplementary material. Yet another study showed that women undergoing testing for hereditary breast/ovarian cancer who received VOUS incorrectly remembered them as being pathogenic (Richter *et al.*, 2013) suggesting that the consent discussion does not always help participants to understand their eventual results.

Similar issues have arisen in the prenatal setting. Research demonstrates that the majority of pregnant women undergoing CMA did not recall being told before their test about the possibility of finding VOUS. Some women given uncertain CMA results continued to worry after delivery and had regrets about having the test (Bernhardt *et al.*, 2013; Hillman *et al.*, 2013). Bernhardt *et al.* (2014) found that clinicians and research coordinators thought participants had unrealistically high expectations that they would learn diagnostic or actionable information and would personally benefit from testing, that they did not anticipate uncertain results and that they expected on-going analysis of stored data. With experience, genetic counsellors and research coordinators learnt to tailor the consent session to address participants' needs, focus on misconceptions and hold an open consent dialogue rather than a more superficial review of the few points included on the consent form.

Another way to improve consent might be for research studies that offer IFs or additional findings to 'bin' them, into broad groups, for example 'clearly deleterious variants with clinical utility,' and 'variants with unknown or no clinical significance' (Berg *et al.*, 2011). Binning could assist with comprehension and make participants' choices more manageable. A problem with this approach is – as mentioned above – variants can be difficult

to classify and classification may change over time. Moreover, even binned findings can be difficult to understand.

Another issue is whether and how participants might amend their consent, for example, if they change their minds about IFs after enrolment. One proposed solution is 'dynamic consent', which would make it possible for people to change options for IFs via web-based platforms (Kaye *et al.*, 2015). Applebaum *et al.* (2014) have also proposed several other models of consent along these lines. One approach is broad consent, where rather than seeking specific consent for a defined list of IFs, the nature of genome-wide testing is explored with participants and they can indicate the types of results they would or would not want to receive. However, as the authors themselves point out, no model is perfect, and researchers must judge which to use by assessing the practicalities and consistency with their perceived ethical obligations to participants. **See also: Informed Consent and Multiplex Genetic Screening**

## Conclusions

In this article, we have summarised some of the key issues from the recent debates about IFs arising from whole-genome approaches in research. It will be important to continue this discussion and conduct empirical research of studies that use genome-wide approaches, especially studies that blur the line between research and clinical practice. In particular, we recommend that further attention is paid to the complex obligations of clinician-researchers and expectations of patients/participants; how any additional findings offered are decided upon and if new conditions can/will be added during the course of the research; how researchers who offer IFs can work with clinicians to communicate these and how the familial implications of IFs are dealt with. Empirical research is needed in particular to explore how best participants can be prepared to receive IFs, their real-life experiences of decision making about them, whether and how different models of consent facilitate informed choices or indeed whether placing ever greater emphasis on consent undermines rather than enhances participants' abilities to exercise their autonomy and be protected from foreseeable harms. Such research has the potential to inform best practice for the management of IFs as the likelihood of finding many different types of them grows.

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