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Defining and managing incidental findings in genetic and genomic practice

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ABSTRACT

The rapidly declining costs and increasing speeds of whole-genome analysis mean that genetic testing is undergoing a shift from targeted approaches to broader ones that look at the entire genome. As whole-genome technologies gain widespread use, questions about the management of so-called incidental findings—those unrelated to the question being asked—need urgent consideration. In this review, we bring together current understanding and arguments about (1) appropriate terminology, (2) the determination of clinical utility and when to disclose incidental findings, (3) the differences in management and disclosure in clinical, research and commercial contexts and (4) ethical and practical issues about familial implications and recontacting those tested. We recommend that greater international consensus is developed around the disclosure and management of incidental findings, with particular attention to when, and how, less clear-cut results should be communicated. We suggest that there is no single term that captures all the issues around these kinds of findings and that different terms may, therefore, need to be used in different settings. We also encourage the use of clear consent processes, but suggest that the absence of consent should not always preclude disclosure. Finally, we recommend further research to identify ways to implement the use of a genome output as a resource, accessible over time, to facilitate appropriate disclosure and recontact when the significance of a previously unclear incidental finding is clarified.

INTRODUCTION

With the increased availability of rapid and cheap technologies, genetic testing is shifting from a targeted approach, whereby specific genes are analysed based on particular symptoms or family histories, to sequencing of an entire exome or genome.[1] The greater the resolution by which the genome is analysed, the greater the probability of finding potential abnormalities that are unrelated to the clinical question for which the test was initiated. Such findings have been called 'incidental findings' (IFs) a term already in use in radiology or biochemistry practice. However, the more that whole-genome analysis becomes a routine approach, the less any finding can be truly incidental. The chance of identifying highly penetrant, pathogenic genetic findings using whole-exome sequencing (WES) of a list of genes not known to be related to the presenting phenotype has been reported as around 1.2%–5% in an adult population,[2 3] and this figure is likely to be greater the more parts of a genome are analysed.[4] It has, therefore, been argued that clinicians, researchers and commercial providers of genome technologies should routinely make testees aware of the potential for IFs.[5] Furthermore, as these techniques gain widespread use, be it in the form of chromosomal microarray (CMA), whole exome sequencing (WES) or whole-genome sequencing (WGS), it is important and timely to consider when and how such findings should be sought and reported, as well as how subsequent clinical interventions can best be organised.[6–9]

In this paper, we review the recent literature about genomic IFs. We include a discussion of the debates around terminology, the types of information to be communicated and the implications for clinical management. We focus mainly on the clinical context, but will also highlight how these issues are subtly different in a research or commercial direct-to-consumer (DTC) setting and review IFs identified in children and adults. Issues around those generated in the prenatal setting merit a separate review.

METHODS

We searched PUBMED, EMBASE and Google Scholar using the keywords 'incidental finding', 'unrelated finding', 'secondary finding', 'secondary variant', 'unexpected result', 'unanticipatable incidental finding', 'unsought for finding', 'unsolicited finding', 'off-target result', 'non-pertinent finding', 'co-incidental finding' and 'opportunistic finding' with 'genetics' or 'genomics'. Inclusion criteria for articles were English-language commentaries, reviews, empirical research papers, consultation documents and guidelines. For professional guidelines (see table 2), we also directly searched the websites of the main professional bodies in North America, Europe and Australia. We also searched relevant journals separately, as well as the references of our initial finds, to ensure we had not omitted any relevant literature. We did not restrict by time-frame, but most of the studies we reviewed had been published in the past year. The earliest article we have referenced is from 2006.

ISSUES TO CONSIDER

Terminology: Incidental finding is not always the best term

There has been much debate about the use of the term 'IF' with alternative suggestions such as unsolicited finding or secondary finding.[10] Standardised terminology, on one hand, could be helpful for consistency in the debate, in management protocols and consent forms.[8] On the other hand, it is likely that no single term would do justice to the wide range of settings and circumstances in which additional novel genetic

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information can be found. Different terms may need to be used by different parties involved (clinicians, researchers, patients). For example, a finding that is unexpected by a patient might be anticipatable by a clinician or researcher simply because they know their field of vision is so broad.[11 12] Terms also need to reflect that a variant, initially with unknown significance, might be reclassified as an IF over time after further investigations.

Whole-genome tests are already quicker and cheaper than the precisely targeted single gene tests from just a few years ago, and so—much like a whole-body MRI scan may find pathology other than the backache with which a patient presents—genomic tests may uncover a range of hitherto unknown disease predispositions. Since broad testing is possible, should the genome be examined 'opportunistically' even if the reason for the test is a specific clinical question? This line of thinking has been introduced by the American College of Medical Genetics and Genomics (ACMG), who recommended testing for 56 clinically actionable conditions every time a genome test is performed.[13] This shift means that some of the terms currently in use no longer capture the full meaning of the findings.[14]

Throughout this review, we use the term IF as an all-encompassing term, as it is the one that has gained the most traction in the debate. Table 1 summarises some of the other terms that have been used to describe additional genomic findings with associated advantages and disadvantages of their use.

Disclosure of findings: clinical utility as a determinant

Much of the debate around whether or not IFs should be disclosed to patients/research participants/consumers is focused around the clinical utility of the finding, which has been defined in a variety of different ways.[20–23] Broadly speaking, clinical utility refers to whether the finding could lead to a medical intervention (ie, treatment, risk-reducing surgery and/or surveillance) that could improve health outcomes. The greater the potential benefit that a medical intervention could provide, the greater the perceived onus to disclose. Potential clinical benefit needs to be weighed against the potential harm of disclosing the IF (such as distress and uncertainty) especially if no specific consent has been given at the time of testing.[13 24] Practical difficulties associated with determining clinical utility are provided hereunder.

Uncertainties about for whom the result has clinical utility, and when.

Many of the patients offered sequencing have been children with developmental delay, intellectual disability or congenital anomalies. These tests can identify mutations in predisposition genes, which might have immediate clinical use and benefit for one of the parents but not the tested child.[25 26] One example, as reported by Lewis and James,[27] is a deletion in the *BRCA1* gene identified in a 5-year-old boy who presented with autism. This result was potentially of relevance to the clinical management of his mother and other family members despite having no clinical utility for the child's immediate health.

International guidelines suggest that children should not be tested for adult-onset genetic conditions until there is a medical benefit or until they can decide if and when to be tested.[28 29] By contrast, the ACMG hold the opinion that the potential

Table 1 Evaluation of terms used to describe incidental genomic findings

Term	Advantages	Disadvantages
Incidental finding	Emphasises that in a setting where genome tests are used to investigate particular signs or symptoms, or search for particular diagnoses, significant findings that do not explain these are incidental to the aim of the investigation.[15]	Finding can provide very significant information, so the term 'incidental' may not do justice to the impact it has on testees, and may trivialise the significance it has. If examining an entire genome then it can be said that no finding is incidental since it is actively sought.[16]
Unsought for/unsolicited finding	Captures the ability of genomic technologies to generate data not necessarily related to the initial diagnostic question.[10]	Findings will only be identified if they are looked for or if some follow-up research is conducted to establish the significance of the variant.[11]
Unrelated finding	Highlights the notion that the finding does not explain the condition for which testing has been done.	Although unrelated to the original investigation, the finding could be related to the current/future health of the tested individual and other family members.
Secondary finding/ secondary variant	Distinguishes between findings causing the disorder for which testing was performed (primary variants) and other clinically important findings (secondary variants).[5]	Does not capture situations where the so-called secondary variant is the only (clinically significant) variant found. Can inaccurately suggest a temporal relationship where one finding is found first, the other the second. The term 'variant' is often used to indicate normal genetic variation or polymorphisms. Using 'variant' to describe predisposition to disease could be confusing.[12]
Unexpected result/ unanticipatable finding	Dividing findings into expected/anticipatable and unexpected/ unanticipatable could remind clinicians that unexpected findings should be discussed with and disclosed to patients in a different way to those associated with the original reason for testing. 'Unexpected' is a term patients can easily understand.[17] Maintaining a division between 'expected' and 'unexpected' helps to emphasise that answers to particular clinical questions are the priority. Any other answers do not provide an explanation to the clinical question.[11 16]	Since the entire genome is being examined, findings that are unrelated to the reason for the test should always be expected or anticipated.[11 15] Expectations of patients, clinicians and researchers are different to each other, so what is unexpected for one might be expected for the other.
Off-target result	Indicates that genomic tests are broader than targeted tests: what is targeted is most clearly seen, but other findings can still be found.[18]	Can give the impression that the result is not correct as it has missed a target.
Non-pertinent/ coincidental	Emphasises that the discovery of some (coincidental) findings is unavoidable (eg, if genes are collocated with those associated with the pertinent finding).	Result may still be pertinent to an individual, just not pertinent to the original question asked.
Opportunistic findings	Emphasises that while looking for particular genomic findings, the analyser looks opportunistically for findings associated with unrelated conditions.[19]	The opportunity the finding gives patients may be opaque to them.

Table 2 Summary of recommendations made by various groups about communication of IFs

Issuing body, country, year	Main recommendations
Clinical setting	
The Presidential Commission for the study of Bioethical Issues, USA, 2013[5]	Professionals should anticipate and plan for IFs, make shared decisions with their patient and communicate a clear plan about what to do should an IF arise.
American College of Medical Genetics and Genomics (ACMG), USA, 2013, 2014[13 84]	1. Labs performing clinical sequencing should actively seek certain IFs and report to clinicians mutations in genes from a specified list for conditions which are considered of medical value for patients' care, unless patients/parents/guardians have opted out of receiving these results. 2. The list of genes includes adult-onset conditions even for children, because the findings could benefit adult family members. 3. Clinicians are urged to minimise the likelihood of generating IFs (which are not part of the list) by targeting the analysis as much as possible.
European Society of Human Genetics (ESHG), 2013[10]	1. A targeted approach to testing or analysis is encouraged to avoid the identification of IFs. 2. Guidelines should be developed about what findings should be disclosed when testing minors. 3. Patient choice should not automatically over-ride professional responsibility. Information about preventable/treatable serious health conditions could be communicated even if patients had chosen not to receive IFs. 4. Guidelines should be established on how and when patients should be recontacted if new evidence about their finding arises.
Association of Genetic Nurses and Counsellors (AGNC), UK, 2013[85]	1. Patients should be allowed to consent to, or opt out of, receiving IFs offered as part of opportunistic testing. Labs will then only test and/or analyse what has been consented to by the patient. 2. Children should not be opportunistically tested for adult-onset conditions.
Public Health Genomics (PHG) Foundation, UK, 2013[86]	1. Patients should be informed before testing that IFs could be identified. 2. Clinical judgement should determine which findings are disclosed, rather than the patient's choice. 3. If opportunistic screening is carried out (ie, an investigation/test which is aimed at generating information ie, not related to the presenting problem), patients should be informed in advance, and should be required to give explicit and separate consent.
The Royal College of Pathologists of Australasia, 2014[87]	1. No consensus on whether, or which, IFs should be reported to the patient. 2. Doctors have both an obligation to consider what the informed patient has requested and to advise the patient of any serious health risk revealed by testing. 3. Doctors also have an obligation to the blood relatives of the patient (although they do not outline what this obligation entails). 4. In cases where patients decline to be informed of 'actionable mutation results', doctors should offer other diagnostic tests and not proceed with genomic testing. 5. Targeted analysis is encouraged to minimise the ethical difficulties of finding IFs.
Berg *et al*, USA, 2011[88]	IFs should be categorised ('binned') with each bin managed differently. Bin 1: Clearly deleterious variants with immediate clinical utility. These should be reported to patients. Bin 2: Variants with a known or presumed association with a disease/trait, but not medically actionable. Their potential return should be discussed by the patient and the clinician at the time of consent. Bin 3: Variants of unknown or no clinical significance. These should not be reported.
Research setting	
The Clinical Sequencing Exploratory Research (CSER) Consortium and the Electronic Medical Records and Genomics (eMERGE) Network , USA, 2014[26]	1. Participants should have the option to refuse IFs. 2. Looking for and confirming IFs would be too resource-intensive, so a requirement to search for IFs is not endorsed. 3. Highly actionable findings that are 'stumbled-upon' should be disclosed to participants. 4. Any obligation to return results does not extend beyond the research funding period.
Wolf *et al*, USA, 2008[60]	1. Researchers have an obligation to discuss the possibility of discovering IFs with research participants and to seek consent for IFs. 2. Findings with definite health or reproductive importance to the research participant should be disclosed. 3. Findings that are not likely to be of serious health or reproductive importance to the research participant, or whose likely health or reproductive importance cannot be ascertained, should not be disclosed. 4. Findings with potential health or reproductive importance to the research participant can be disclosed, unless participants choose not to be informed of such findings. However, researchers have no obligations to disclose findings. 5. In studies involving children/adolescents, both parents/guardians and the older child/adolescent should be asked in advance whether or not they would like information about IFs. ▶ In cases where parents/guardians agree to receive IFs and the older child/adolescent disagrees, the information is disclosed to the former, highlighting the importance of further clinical evaluation. ▶ Cases where the older child/adolescent wants to know and the parent/guardian does not should be evaluated on a case-by-case basis. 6. Children/parents/guardians should not be informed of adult-onset conditions with no interventions in childhood.

Continued

Table 2 Continued

Issuing body, country, year	Main recommendations
Presidential Commission for the Study of Bioethical Issues, USA, 2013[5]	1. Researchers should discuss the possibility of identifying IFs with participants and explain whether and how IFs will be disclosed. 2. Researchers should decide in advance what types of findings are returned, and whether or not research participants can choose to not receive such findings. Research participation can be declined if the participant does not accept some IFs will be returned. Research review bodies should be consulted about difficult cases. 3. Researchers do not have an obligation to actively look for findings which are outside the aim of the study.
P3G international paediatrics platform group, International, 2014[89]	1. IFs that predispose the child to develop an adult-onset disorder, even if accidentally discovered in the research process, generally should not be returned. 2. Where there is potential benefit to the wider family, decisions should be made on a case-by-case basis.
Wilfond and Carpenter, USA, 2008[90]	1. Clear, proximate medically actionable IFs should be disclosed to both parents and older children/adolescents. 2. In particular situations, a result may be disclosed to only one party. 3. Families should be asked for their preferences regarding IFs with no clear and proximate clinical importance, but researchers have no duty to disclose such findings. 4. IFs with no clear and proximate clinical benefit should be discussed by a research review committee, but it is generally recommended that they are not disclosed. 5. The child's best interest should be paramount, while trying to respect the requests of parents as much as possible. 6. IF management should be discussed in person, not confined to consent forms.
Commercial setting	
The Presidential Commission for the study of Bioethical Issues, USA, 2013[5]	1. Consumers should be informed of the possibility of finding IFs, and which findings will and will not be disclosed, before testing. 2. DTC companies should collaborate to develop best practices concerning the type of findings that are looked for and disclosed and standards for referral for clinical services. 3. DTC providers who discover clinically actionable IFs should provide consumers with educational information about the finding and advice about how best to seek care from a clinician, or refer them to a clinician.

DTC, direct-to-consumer; IF, incidental finding.

benefits to adult family members outweigh the potential harms of disclosing findings that do not have immediate clinical utility for the child, at least in the near future when parents are not likely to otherwise have access to genomic tests. The ACMG also argue that the child does benefit because a severe adverse health outcome is potentially prevented in her parent.[30] They, therefore, recommend that children undergoing WES/WGS are opportunistically tested for mutations in genes associated with increased risk of cancer in adults.[13] Although Yu *et al*[31] found 68% (573/840) of genetic health professionals agreed that the results from the ACMG list of genes should be reported, there have been many critics of this approach, who disagree and state that a child's best interest should be the only reason for testing and disclosing a result.[32–34] These disagreements further evidence the tension that occurs when tests are no longer targeted to investigate specific questions. Once a result is available, clinicians might feel a need or obligation to disclose it, even if they would not have ordered that specific test in the first place.[35]

Clinical validity

Another issue to consider is the clinical validity of findings, that is, the accuracy with which a particular finding predicts the presence or absence of the underlying condition. The clinical validity (present or future) of an IF can be unclear if the expressivity is known to be variable (eg, deletions where the reported phenotype ranges from entirely normal to neurodevelopmental delay).[36] Likelihood of disease can depend on other genetic, environmental or stochastic factors that have not been, or cannot yet be, determined, leaving a degree of uncertainty.[37] The finding may, therefore, give a very incomplete prediction of disease. Such variants may have been known about, but not offered as a clinical diagnostic test, in the past. Should they now be reported just because they have been found?

Ascertaining the clinical validity of a finding could also be complicated by the mislabelling of benign changes as pathogenic,[38] or through different bioinformatic pipelines assigning different clinical significances to the same variant.[39] Although some of these can be resolved through alternative confirmatory techniques, false positive IFs can still arise, and it has been argued that patients should be told about the possibility of such results during the consent process.[40]

Novel findings not previously described in the literature

Some findings may appear possibly pathogenic (eg, a deletion found on microarray not previously described), but have, as yet, no evidence for pathogenicity. Functional studies of the finding or familial segregation studies might assist in clarifying the clinical significance of a finding,[41] but may, equally, give indefinite answers or, because they require testing and surveillance of family members, be too difficult or resource-intensive to perform. The uncertainty and extra steps needed to find out the significance of a finding will warrant careful communication, both with the patient and potentially their family.[42]

Personal utility

Some results will lack clinical utility because there are no available medical interventions. For example, Presenilin 1 or Huntington gene mutations can cause early onset dementia, but there are, as yet, no known medical interventions that alleviate the course of the disease. Another example is carriership of an

autosomal recessive condition, which could have implications for reproduction but not for the health of the carrier. These findings can, however, be perceived as having personal utility. That is, individuals could still consider these findings useful to know about because the knowledge would lead them to choose different reproductive options or make lifestyle and health behaviour changes.[43–46] Should then results be disclosed, regardless of the lack of available medical intervention, because of the potential impact on people's life choices?[47] Some argue against such disclosure because of the limited resources to analyse and return all IFs in a way that patients can understand,[48] and evidence that receiving genomic information has little impact on health behaviours.[49 50]

Management of IFs in different settings

Although boundaries between settings are sometimes blurred, whether an IF is generated in a clinical, research or commercial context will likely affect its management.

Clinical setting

A genetic investigation is usually done in the clinical setting because certain signs, symptoms or family history of disease suggest a possible genetic aetiology. As the genetic code is investigated in more detail, healthcare professionals will need to consider more downstream consequences of testing. So-called mainstreaming means that testing will be done in settings where clinicians have little experience of genetics/genomics. Professionals from a particular specialty may also feel unequipped to consult about IFs that fall outside their speciality. For example, an oncologist discovering a risk of sudden cardiac death will likely refer for cardiology opinions.[9]

Studies that have sought patient or parental views about disclosing IFs from whole-genome tests show that most respondents would want to be told about *any* result generated, because the perceived advantages (be they based on medical benefit or personal utility) outweigh the disadvantages of knowing.[17 44 51 52] Findings from these studies could be poor predictors of actual decisions, since participants had not received IFs, and their views were gathered in response to hypothetical situations.

In practice, patients do not always pay sufficient attention to, or process information about, potential IFs during the consent process because they, and perhaps their clinician, perceive the likelihood of one arising to be small[53] and because their main concern is to achieve a diagnosis.[7] Indeed, when given a hypothetical case involving uncertain findings and IFs identified in a child, some clinicians did not find it important to discuss with parents the potential for such discoveries to be made.[53] Clinicians have a duty to consider the welfare of their patients: if patients decide they do not want any information about IFs, clinicians might be faced with a dilemma about whether or not to disregard the patient's wishes to not know and disclose an IF that has a proven clinical intervention, particularly one that could have medical urgency.[7 17 54 55] Yu *et al*[31] found that in clinical practice 68% (239/349) of clinicians offered to return IFs for Mendelian conditions, 47% (164/349) for adverse drug responses and 45% (157/349) for autosomal recessive carrier status (157/349). Eighty-one per cent (673/836) agreed that the patient/parent's preferences should guide which IFs should be offered for return. However, Clayton *et al*[56] argue that clinicians could in the future face liability if they do not disclose medically actionable IFs. The ACMG have expressed a similar concern.[57]

There is also the question of whether laboratory scientists have an obligation to report clinically relevant IFs to the patient's clinician once found and whether they might be held liable for not doing so. Again, the degree of targeting is relevant here: non-disclosure of a clinically relevant IF could incur liability, even though with targeted testing it would not have found it in the first place.[58]

The costs associated with conducting additional diagnostic tests, possibly in several family members as well as clinical follow-up, also need to be taken into account.[5 59] Discussing all possible findings and their potential significance in detail would have major practical consequences for any health service.[8 42] Identifying, interpreting and communicating IFs could incur economic costs and will increase the use of health service time, effort and resources.[9] Indeed, in a survey study with genetic healthcare professionals, Yu *et al*[31] found that 65% (518/799) thought the biggest challenge in the return of IFs was lack of time and expertise among clinicians.

Research setting

Researchers' obligations include ensuring individuals exercise a free choice to participate in research, and that any harm in so doing is minimised. This emphasis is different to the predominant consideration of welfare in a clinical setting. Although there is growing support for researchers' duty to disclose IFs with clear, proximate clinical significance,[60–63] disclosure is still less of a default position than in clinical practice. For example, two current UK research studies state explicitly that IFs will not be disclosed: the 'EACH study', where participants are offered prenatal array comparative genomic hybridisation testing[64] and the 'DDD study', where diagnoses in children with severe undiagnosed developmental disorders are sought.[65] By contrast, Gliwa and Berkman suggest that, in certain circumstances, researchers do indeed have an obligation to actively look for and disclose IFs.[66] These include situations where disclosure would be lifesaving, the participant would have no other way of getting the information and the search would not burden the researcher in terms of time, effort and financial and other resources. Ross and Reiff argue that such a duty should only exist if a set list of variants of known clinical utility is generated and if participants choose to receive the results.[67] Others have argued that a duty to look for IFs is not realistic and point out that were finding and returning IFs to become the standard in research, malpractice litigations would increase, placing a significant burden on any research where IFs can be uncovered.[68–71]

Empirical research by Fernandez *et al*[51] showed that most researchers do not feel obliged to look for IFs with clinical utility in genomic studies but, once identified, think research participants have a right to receive them. Less than half the researchers indicated that their research ethics board required an offer of results, or to provide a detailed process for managing IFs. Similar to studies in the clinical setting, a survey of the general US public demonstrated that the majority would like to be told of IFs if they were participants in a genetic research study.[72] An international survey by Middleton *et al*[73] revealed that although genomic researchers, genetic health professionals, laboratory scientists and members of the public are generally supportive of disclosing or receiving IFs from research studies, they do not believe researchers have a duty to search for them. Appelbaum *et al* found that both researchers and participants expressed concerns that a focus on IFs in the consent process and long consent forms could tax participants' concentration or cause them to feel overwhelmed.[55] Discussions about the return of IFs in the consent process can also lead to a 'therapeutic misconception'—the perception that taking part in research will provide individual clinical benefit.[74–78]

Some test providers will have a dual-role as a clinician and researcher, making their obligations particularly complex. For instance, participation in research is offered to some patients to get a diagnosis or prediction through a test currently unavailable via the health service.[53] Even with a detailed consent process, making the distinction between research and clinic clear to testees is not always easy or realistic. Hence, participants might not understand if and what results will be returned.[60 79]

Commercial setting

DTC genetic testing in some cases bypasses the relationship with a clinician/researcher at the point of testing and receipt of results. Some have expressed concern about whether consumers of DTC genomic tests, are offered adequate pretest information and psychosocial support.[80] This concern also exists in the clinical and research setting, but is amplified in the commercial setting where consumers may receive results without an explanation from a clinician or researcher. The rise of such testing has also raised concerns about consumers turning to and overburdening the health service to interpret test results not clinically indicated.[81 82]

Testing companies will usually stipulate whether they reveal targeted or broad information about, for example, ancestry or health-related risks, so certain results could be considered incidental if there is no prior indication to their existence from, for example, a family history. However, whereas in clinical and the research settings testing is initiated to identify the cause for a particular condition, DTC testing might be initiated with no particular condition in mind. It is, therefore, questionable whether the term IF, or any of the related terms, is appropriate in this context, where testing is not aimed to answer a particular question. Although a major provider of DTC genetic testing has currently suspended its testing to determine health risks while it is scrutinised by regulatory authorities,[83] we consider it likely that some form of DTC testing about disease predisposition will be available again in the future.

Guidelines and recommendations for different settings

Recent international guidelines, position papers and well-cited recommendations about the disclosure of IFs to patients, research participants or consumers, are summarised in table 2. Some specifically address the issue of IFs, while others mention IFs as part of more comprehensive documents on WES/WGS.

As demonstrated in table 2, there is general agreement that patients/research participants/consumers should be informed before testing about the findings that will or will not be disclosed. Furthermore, there is agreement that clear, proximate, clinically important findings should be disclosed. However, where IFs have no clear, proximate clinical significance, there is less agreement about how much choice patients/parents/guardians should have over which findings to receive. Whereas opportunistic screening is offered in the USA, it is not currently endorsed by professional organisations in Europe.[10]

Genomic IFs versus IFs in other areas of medicine

IFs are not unique to genomic medicine. An isolated pulmonary nodule identified in about 10% of patients undergoing cardiac computerised tomography is just one example from radiology.[91] Nevertheless, there are two aspects of genomic IFs that warrant special consideration. First, IFs in one person may indicate risks to family members, raising issues about communication to others. Second, some genomic IFs will predict clinical significance in the future rather than current ill health, throwing into question the appropriate stage of their communication and possible duties health professionals have to recontact patients.

Familial implications

Although whole-genome approaches promise to help deliver ever more personalised medicine, any strongly predictive finding can also predict ill health in family members.[42] For example, a BRCA IF discovered in a child could be clinically relevant to other family members well before it impacts on the care of the child. Family structure might, therefore, influence clinical management of an IF. For example, an IF in a patient with no apparent at-risk relatives might be managed differently than if relatives might benefit from an intervention.[24]

Where the clinical significance of an IF is not certain, exploring clinical features in family members may be necessary to determine its pathogenicity and clinical significance.[41 42] Seeking the cooperation of family members for testing can be difficult,[54] both in terms of practical issues of contacting relatives as well as explaining the need for testing. Studies of intrafamilial communication of genetic information demonstrate that people do not always share information with family, despite their intentions, because they feel guilty, are not in contact, or feel unable to communicate such complex information accurately. Patients also inform certain members of their nuclear family more than distant relatives.[92 93] Intrafamilial communication of IFs might be even more difficult given there is likely to be no family history of the condition implicated by the IF.

Studies that have explored theoretical intentions to share IFs have shown that individuals feel a responsibility to tell relatives, including extended family members, because the information could benefit them. Others have been more hesitant to pass on 'less medically certain' information and would want to consider how family members would react to the information before imparting it.[44] Participants have also raised a perceived right to be informed about a gene discovery in a sibling, even in the absence of effective treatment or prevention.[51 94] To date, there is little empirical data about actual sharing and barriers to sharing in families where IFs have been identified.

Recontacting

Questions may also arise about whether, and how, people should be recontacted in the light of new evidence about their IF. Furthermore, recontact may be required for young adults in whom an adult-onset IF was identified in childhood. Parents and clinicians have expressed concerns that an IF with relevance for an adult-onset condition might be lost over time.[17] Questions arise as to when recontacting should occur: at a set age, when the child reaches adolescence or at a time when the information is clinically relevant. The ACMG (2013) recommends that patients should be informed of policies regarding recontact when knowledge is gained on the significance of IFs, but note that a legal duty to recontact would be difficult to implement.[56]

The infrastructure for such extensive data storage, analyses of variants and follow-up consultations does not exist, and would be costly and logistically difficult to implement,[95 96] particularly if trying to locate people years after they were tested. An additional issue is raised about who, if anyone, would be responsible for notifying at-risk relatives should information relevant to them be found.[56]

Solutions to issues about recontacting have been proposed. Driessnack *et al* found that the general public and parents of children undergoing genetic testing thought parents should be responsible for keeping track of information about their child

and that the child's medical records should follow them into adulthood as a backup. Medical records were viewed as a reliable place to store information about IFs.[97] Yu *et al*[98] have offered a two-part solution. First, they suggest, like Biesecker,[99] that the genome result should be viewed as a dynamic resource that does not have to be disclosed all at once but can be dipped into over time. Second, they suggest that patients should be permitted to self-manage their genomic information and engage clinicians if, and when, they want to enquire about screening at different times in their lives. Otten *et al* (personal communication, 2014) piloted novel apps or web-based approaches to allow patients to get updated information without expensive clinic appointments. Giving responsibility to patients or parents for contacting clinicians can be seen as a pragmatic solution to the current lack of infrastructure for healthcare services to reliably recontact testees. This solution has been supported in one study by members of the public, who expressed a perceived responsibility to check their original test results with genomic developments.[48]

KEY QUESTIONS THAT NEED ADDRESSING

Genomic technologies have arrived and are here to stay. Sequencing costs may be falling, but analysis, interpretation and communication remains an expensive bottleneck in clinical translation.[5] Thus, a pressing question is how current practice can best adapt responsively and appropriately to the complexity and number of results from advanced genomic tests. A practical solution proposed by many is to introduce filters at the analysis stage to mask 'undesired' results. Individuals could be told that, although a whole-genome approach is to be used, only certain aspects of the output will be interrogated or examined. Some UK labs have already adopted this approach in CMA testing: only imbalances above certain sizes will be sought and reported.[100] Targeting the testing will minimise (but not eliminate) the chances of IFs,[10 87] but broad testing will improve the diagnostic rate over targeted analyses. As suggested by Green *et al*,[101] 'rather than exceptionalise the return of incidental genomic findings, clinicians and patients should embrace them as adjuvant information of potential utility and as a welcome component of modern medical practice'.

As in the field of medical imaging, the management and communication of IFs requires international consensus rather than ad hoc approaches.[102] Our review of the literature suggests there is widespread agreement that clearly pathogenic IFs identified in clinical practice, when treatment or care (present or future) is available, should be communicated.[74 88] We recommend that consensus is also developed about communication of less clear-cut results, definitions of actionability, and policies about recontact in the light of more definitive information. For non-genetic health professionals, in particular, education and training about how to interpret and communicate IFs with patients is needed.[9]

Current recommendations about consent range from offering menu-type options on consent forms[103] to a blanket disclosure policy to return all genomic findings, regardless of their significance.[104] We consider that consent to the general possibility of receiving clinically significant information that is not related to the clinical reason for doing the test is possible. This process should include discussions about alternative forms of testing should such consent be refused, or how any findings not disclosed should be recorded in patient records. We think that consent for disclosure of IFs should be sought where possible, but its absence should not necessarily preclude disclosure in specific circumstances. As Dondorp *et al* point out, patients cannot be expected to give consent to an almost infinite number of possible outcomes from testing. How best to facilitate adequate consent will need to be worked out and evaluated in practice.[105]

CONCLUSIONS

Our review has summarised the recent debate and literature around IFs arising from whole-genome technologies. The term 'IF' does not accurately cover all the situations in which it has been applied, yet proposed alternatives have their own problems. As the use of technology changes in practice, terminology will likely shift to diagnostic and opportunistic findings,[13 19] although surprise findings that reveal unsuspected diagnoses or predispositions may still arise even if opportunistic screening is targeted to specific pathogenic variants. Where patient/research participants and healthcare professional views have been sought they have largely been of hypothetical situations, so it will be interesting to see whether these views hold as situations where IFs are found become a more widespread reality.

We recommend that further attention is paid to the following issues:

1. Using the genome result as a resource, accessible over time rather than necessitating disclosure of information all at once. The ethical, legal and practical issues around storing results that are not disclosed immediately would, however, need careful evaluation.
2. Management of the familial implications of IFs; who, if anyone, has responsibility for their disclosure to family members, and when this would be appropriate.
3. What level of risk or certainty should be associated with potential IFs before disclosure is considered.
4. Being clear and specific about what is meant by any of the terms listed in table 1, taking into account that no one term will suit all situations.
5. When the output of genomic investigation becomes part of a patient's records, and what obligations ensue as a result.

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Defining and managing incidental findings in genetic and genomic practice

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