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Management of Incidental Findings from Genetic Tests: Perspectives of Ethics Committee Members

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Abstract

New genomic technologies, whilst allowing comprehensive and cost-effective access to disease-causing mutations, also increase the possibility of incidental findings unrelated to the original research question. These findings may have health, reproductive or familial implications for the research participant concerned. There are diverse opinions regarding the obligations of researchers and appropriate management strategies regarding how or whether to return this information to research participants. As the empirical data on which these arguments are based is still fairly limited, we undertook a qualitative study, using a thematic analysis approach, to explore the topic further. We interviewed members of UK NHS research ethics committees to ascertain their experiences regarding genetic incidental findings, as well as their opinions regarding future challenges and management. The interviews were transcribed, coded and analysed for common themes. Three themes emerged; facilitating participant consent, supporting the validity of consent, and risks and rights. Ethics committee members were aware of the issues raised by genetic incidental findings despite limited practical experience in the projects they have assessed. There was no consensus as to how information should be presented to potential participants during recruitment for research involving genome-wide technologies, or whether blanket or checklist-based consent was most useful. Participants also discussed the difficulties in balancing the rights and obligations of research participants, their families, researchers and clinicians when considering the return of incidental findings. Some supported overruling patient consent in order to return clinically actionable incidental findings. In the absence of national guidance on these issues, the lack of consensus evident in this study could potentially lead to disparity between research ethics committees in the way genetic research studies are appraised. A wider discussion on the suitability of the current informed consent model for complex genomic research may also be required.

Keywords Genetic incidental findings; Research ethics; Ethics committee; Informed consent; Genome testing

Introduction

The past decade has seen a transition towards new testing technologies that focus on the genome as a whole, driven by affordable sequencing technologies [1,2]. As costs of exome or genome sequencing rapidly approach the cost of a single gene test, personalized medicine applications become more feasible [3]. However, the use of whole genome or exome sequencing carries a risk of creating incidental findings (IF).

A number of ethical, legal and clinically practical issues are raised by incidental findings, defined as "a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study" [4]. The issues concerning the obligations to search for and report IF have been extensively discussed in the literature in the form of opinion articles, commentaries and ethical discussions [4,5-9], however there is a paucity of primary research data available for analysis.

A systematic review of empirical research concerning the management of IF [10] found only four studies that were relevant to the specific research question. However, the field has advanced somewhat since the publication of the systematic review. The Deciphering Developmental Disorders (DDD) study at the Wellcome Trust Sanger Institute has an ethical sub-group that has conducted a large international survey of attitudes to the return of results from genetic testing, including IF. Initial findings suggest that genetic health professionals (53%) were the least likely to think that IF relating to life-threatening, untreatable conditions should be shared, compared to the public (69%), genomic researchers (72%) and other health professionals (77%) ($p<0.0001$). Participants in all groups believed that genomic researchers should remain focussed on their research question and not actively seek IF. An appreciation of the difficulty of translating genomic data to the clinic may underpin why genetic health professionals were the most cautious regarding return of IF.

Those findings are in concordance with a survey examining the opinion of clinical genetics health professionals conducted at the American College of Medical Genetics and Genomics (ACMG) Next Generation Sequencing Workshop in 2012 carried out by Lemke [11]. The authors report that less than half (44%) of respondents would want to hear about untreatable adult-onset IF themselves and around half (52%) thought this information should be returned to patients. However, this figure rose to 96% (both for their own desire to know and their opinion about returning results) if the IF was related to an adult-onset condition that was clinically actionable. Downing et al. examined the opinions of genetics specialists and found a lack of consensus regarding the return of IF [12-15]. This qualitative study gave an insight into the reasons behind clinicians' opinions of IF and complements the quantitative study of Lemke et al. The possibility of overloading patients in the pre-test stage with information concerning potential harmful results was raised as a concern, along with the

implications of allowing patients to opt-out of receiving what may be clinically relevant and actionable information [11]. While a majority of participants supported overarching guidelines to deal with IF management, they also desired flexibility to adapt to the nuances of individual cases.

The views of Canadian genomic researchers about the return of IF in a paediatric setting were examined by Fernandez et al. [16]. Only a minority supported actively searching for IF (37%), but 68% believed that when IF were discovered they should be disclosed, in accordance with adult studies. There was also majority support for the return of genetic IF to siblings of participants (62%) and this support was strengthened if the condition was treatable (76%).

A common theme throughout all studies described above was the need for guidance and regulation. It is clear, therefore, that there is an urgent need for more primary research into the management of IF generated by these new technologies. There is a tangible risk to the patients' medical management, psychological well-being and family relationships if these issues are not considered and appropriately dealt with prospectively.

In the UK, NHS Research Ethics Committees (RECs) are the gatekeepers to research involving patients within the NHS. Potential research projects must be submitted to a regional ethics board, who consider the ethical arrangements and potential risks to participants. It is therefore extremely important in an era of increasing genomic research that the perspectives of REC members are considered. Similar studies concerning only the chairs of Institutional Review Boards (IRBs) have found concerns with changing participant preference over time, fears regarding result accuracy and the complexity of the consent process [14]. Comparison of the perspectives of ethical committee chairpersons and genomic researchers found that chairpersons were more in favour of prescribed guidance, in advance of research, rather than ad hoc decisions [15]. However, chairpersons may not be representative of the wider committee, which in the UK includes a range of experienced health professionals and lay members. In the current study, we therefore decided to explore the views of both lay and expert REC members to ensure we encompassed a wider range of perspectives.

Aims and Objectives

The aim of this study was to establish the views and expectations of Research Ethics Committee (REC) members in relation to dealing with the occurrence, or possible occurrence of genetic or genomic IF in a research setting.

The objectives were:

- to explore the attitudes of REC members regarding the possibilities and handling of IF;
- to determine the current approach taken regarding IF within a research context;
- to explore the views of REC members as to whether sufficient guidelines exist, and whether they are being put into practice;
- to obtain the opinions of the REC members on issues concerning obtaining informed consent and the anonymisation of participant data.

Methods

Design

As this was an exploratory study we used a qualitative descriptive approach based on thematic analysis.

Population and sample

Members of UK NHS RECs were identified through a request made to the chairperson of each committee. Members were purposively recruited to participate in a semi-structured telephone interview. We recruited until data saturation was reached [17]. A total of 26 participants were recruited from a wide range of committees in England, Wales and Northern Ireland. Both expert and lay members were recruited to give a maximum variation sample.

Instruments and data collection

Interviews are a suitable method of collecting qualitative data [17]. Telephone interviews were conducted by a single researcher to minimise cross-interview variation. A semi-structured interview schedule focussed on REC member perspectives, experience and concerns were used to lead discussion. The interviews were recorded and transcribed verbatim by an experienced transcriber.

Interview data analysis

Interview transcripts were analysed using thematic analysis techniques [18]. Codes were individually generated by two independent researchers who then met to discuss discrepancies until consensus was achieved. Common categories and themes were identified and agreed. Once consensus was achieved across all transcripts, a meeting was conducted with a third experienced researcher in the field who evaluated all the codes and considered the suitability of the themes identified. In this manner, agreement on codes and overarching themes was achieved in a robust manner.

Results

The results are presented below. As the study participants frequently referred to other research participants, to prevent confusion we will use the term 'REC members' throughout to describe our participants.

As a process issue, an interesting observation regarding the apparent consideration given to each question was noted by the researcher. All interviews were carried out by a single researcher who was then able to compare non-transcribed data such as pausing, laughter and also the relative duration of each interview. REC members had deliberately not been presented with the questions in advance, although some admitted to having read around the subject prior to interview. Interview duration ranged from a little over 5 minutes to more than an hour. Individual REC members tended to either give short concise answers with little or no explanation to questions or long, detailed responses working through their mental processes and explaining the ethical concepts involved.

The findings are presented under three overarching themes.

Facilitating Participant Consent

Access to information

REC members acknowledged the complexity and impact of IF and were concerned about how information was presented to potential research participants. Observations were made that it is not enough to simply provide information to facilitate informed consent, it must be in a format that is accessible and understandable. Participants felt that any ambiguity in the participant information sheet and consent form could lead to confusion as to what the participant was actually consenting to and could create difficulties downstream if expectations were different from the reality of the project.

As well as making the information easy to understand, it was identified that the particular language used must be carefully considered. The use of the term 'risk' was considered to denote a universally negative connotation that could adversely affect a participant's understanding of the consequences.

(17) "they only hear risk, they don't want to hear small or tiny, they just hear risk."

Prior information and discussion

A large number of REC members suggested that many problems and ethical dilemmas regarding return of IF could be avoided with sufficient provision and discussion of information prior to consent.

(5) "[I]think again this should be in the PIS [participant information sheet] in terms of what is going to happen if they do find things."

REC members were open to a number of different strategies for dealing with IF, as long as these were clearly identified ahead of time.

(14) "I think it is better to cover that by saying, you know, in the event of something unexpected being discovered we will you know….refer you to the appropriate person for that permission to be discussed with you."

However, REC members thought that at present the information provided was insufficient to make potential participants acutely aware of all the ramifications associated with consenting to take part in research studies.

(3) "they should be made aware of that [the possibility of an incidental finding] because a lot of them don't realise that something like that could come up."

Supporting the Validity of Consent

The second theme was concerned with supporting the validity of consent. It was apparent from the data that REC members were aware that consent could often be obtained, but if that consent was based on incorrect assumptions or unethical practices then it lacked validity.

Level of information and consent

REC members were concerned that, despite agreeing to take part in research, participants may not fully appreciate what they were consenting to if a broad consent model was used.

(23) "I am worried that at some time in the future that there could be tests carried out which the patient currently consenting cannot consent to because they cannot envisage that they may happen."

REC members were also concerned that patients should not be misled as to the aims and scope of the research in which they were participating. In particular, participants should not be under the impression that taking part in research was a good way of receiving personal health information.

(19) "you tell them what we are looking for, don't tell them we are giving you some sort of free diagnosis of your health."

A small number of REC members were very concerned that it may not even be possible to obtain informed consent for genome-wide technologies, given the complexities and uncertainties involved. They based this on their experience of the difficulties already experienced with obtaining consent for much simpler procedures. One REC member when asked whether informed consent was feasible for these tests responded:

(11) "No. My instant reaction to that is no. I think informed consent is a bit of a joke in many instances. When I get informed consent on people for operations I think half the time they don't know what I am going to do or what I am doing and that's a simple you know, a simple back operation or head operation. But no informed consent is impossible, it's a joke.

It's a complete waste of time. You know I spend 15 minutes explaining what an operation entails, what I am going to do, what the risks and everything and then they come in on the morning of surgery and they say 'What are you actually doing?'. They have heard nothing. People don't have a clue. Informed consent is a joke. We still insist on it but…"

Patient autonomy

The concept of patient/participant autonomy was discussed frequently by REC members. Observations were made that there could be no 'one size fits all' policy regarding consent for IF feedback, as this would infringe upon individuals' rights.

(18) "a case by case basis is the best way to do it because each individual person has a different set of preferences. "

A number of REC members thought that whatever the researcher wanted to do required permission from the participant. If a situation where IF might arise could be envisaged, then it should be discussed as part of the consent procedure. If this did not occur, then some REC members felt that the researcher was restricted in their actions.

(16) "not without asking them, not without their permission."

Some REC members were unwilling to be complicit in the keeping of secrets and believed that any kind of paternalistic decision-making would infringe on the rights of participants.

(7) "I think the participants/patients have the right to exercise their autonomy and researchers shouldn't deliberately hide any information from them, providing they have expressed their wish to know."

Others, however, believed that in certain situations it was appropriate to restrict participant autonomy by removing their ability to decide on the level of their consent.

(14) "So therefore you have somebody who is clinically competent to make a diagnosis and they see an anomaly that could treated but the participant has said they don't want that feeding back. I think that is deeply problematic for the clinician doing those reviews. I think it is not consistent with what would be seen as the standard duty of care in

that context. So really you can't give patients an option, participants an option, in that circumstance."

(17) "The professional actually has a duty of care to the individual if the finding is deemed serious enough."

Practicalities of a checklist

A number of authors have suggested the use of checklists on the consent form to enable participants to choose what information they would wish to receive. Different forms ranging from lists of individual conditions to grouping conditions based on severity, treatability, lethality and other factors have been proposed. When asked about the use of checklists during the consent procedure, many REC members were concerned about the practicalities of how this would work in practice.

(7) "If you write out a checklist for participants to consent to for example, so minor, moderate or major, the question is how would you define those terms?"

(10) "Are you going to list every possibility? That could end up being quite a long list couldn't it."

Other REC members were concerned about the burden that both creating and considering such a checklist would place on researchers and participants respectively.

(11) "That might put an intolerable burden on both the researcher and the subject because you know to try and think about all that while you are deciding whether to take part in the study or not would be very onerous."

Others were also concerned about the effect of merely being presented with such conditions on an information sheet. It was feared that listing serious life-threatening conditions could discourage people from participating altogether, or that they may participate and live under a cloud of fear, assuming they would be likely to develop some or all of these diseases.

(12) "I think there might be some people who if they have put a cross against say Huntington's again would go through the rest of life thinking they were going to get Huntington's and that would be absolutely disastrous."

Information and consent

Many REC members were firmly of the opinion that the correct strategy in advance (regarding sufficient information provision and discussion with participants) would save much confusion and misunderstanding downstream. The idea of IF, these REC members suggested, should never come as a surprise to participants.

(2) "you don't find an unexpected genetic result in a research situation unless you are doing genetic tests on people and so that can be discussed or they can give their opinion on that before you even set about doing the genetic test."

Furthermore, it was suggested that the strategy for dealing with IF should be obvious ahead of time and part of the research project protocol. It was at this stage that the REC committees should be involved with discussing the mechanism of feedback rather than having to make difficult ethical decisions after the fact.

(26) "it is something that is already stated at the beginning, so I don't think it should involve the ethics it is something that the ethics should consider in the PIS form and then see the mechanism of coming back to the patient or participant."

There was a general consensus that a number of different approaches and strategies for dealing with IF could be justified, as long as they were clearly identified before obtaining consent. One REC member even outlined a strategy they had encountered that they believed was a good approach, but commented that it wasn't a common approach.

(25) "on some proposals we find people saying we won't normally tell you about your genetic results, however if there was something that came up that we felt would be useful for you to know in terms of your clinical care then would you like to know about it. And I have seen that and I think that it is quite a good default position but very few people do it."

Risks and Rights

The third theme related to the various risks and rights involved in IF discussions. These may involve the participant, the researcher, the participant's family or the wider public.

Right to (not) know

There was a strong feeling amongst REC members that participants in research had a right to know information about their health and wellbeing, with some going as far as to say researchers had a duty to inform them about "their bodies". There was a collective unease that researchers may be in possession of information not available to participants.

(22) "thinking of it as a participant, I don't want the researchers to know and me not know, of course I want to know."

This was demonstrated on both the behalf of the participant having a right to know their own information, but also framed in regards to the burden on researchers if they withheld sensitive information from participants.

(2) "I don't think we should keep biological secrets about people."

It was further suggested that there may be a moral pressure on researchers, due to participants' expectations (when consenting to take part in research) that they would receive beneficial health information.

(14) "there isn't a consensus but there is certainly a strong argument from some quarters, a kind of legitimate claim from the patient expecting to have feedback on things and therefore that might put some kind of moral pressure on researchers you know who are taking the sort of blinkered strategy."

However, REC members also recognised that the right to genetic information needed to be adequately explained to and understood by participants and the wider public alike, before fully informed decisions regarding consent and IF return could be made.

(14) "groups that represent public opinion that say we have a right to genetic information, well so yes you do, but let's have a good understanding of what genetic information is and let's understand what might be feasible to get to manage incidental findings in these complex contexts."

Balance of rights

The concept of balancing different rights was discussed frequently by REC members. There was an acknowledgement that the issue of IF was not a simple ethical issue that could be easily and satisfactorily resolved for all participants. Instead, a balancing of different rights, both of participants and other stakeholders (such as family and researchers) was needed to achieve a practical solution.

One participant reflected on just how complex these scenarios might be and how one might logically make their way through the issues.

(22) "whenever you have things like this which are awkward and I suppose if you are going to give, say about this breaking, as it were, somebody's express wishes on the consent form, all of those things, it's a bit like doing it in a counselling session, it's OK but you do have to say that is what you are going to do at the outset and then ethically you feel fine because so long as you have taken care of coercion and mental capacity then that's ok and people have consented and given detailed information that says 'we are going to be looking for those things, you said you don't want to hear about things which is fine so we won't', except, the same as you would in a counselling or a doctor's consultation it's completely confidential unless I find out that you are going to harm somebody else or harm yourself, in which case I'm afraid I'm going to tell."

Others believed that the issues at hand needed significant thought and did not feel confident expressing an immediate opinion.

(11) "that one is going to take a week to think about. There are so many ins and so many outs there with other people's interests and everything."

Some REC members were concerned about the difficulty of weighing the different rights of a participant themselves.

(11) "personal autonomy up against I don't know what personal welfare. Yes I was worried I hadn't thought about this enough and clearly I haven't."

Others were concerned about the risks to other people if participant confidentiality and autonomy were placed above the right to information and health of others.

(8) "confidentiality is not absolute and there will be occasions when you have to weigh the need for a confidential health service against the risks to people"

The idea of applying a public interest test, when deciding what to do with IF that could provide clinical benefit to the participant or others, was discussed. One REC member further suggested that this should only apply if a participant was still alive but that post mortem their wishes should be respected.

(8) "If a person hasn't died and they have stated a preference I think it is possible to override that on this public interest test."

The issue was further complicated by one REC member conceiving a situation whereby the capacity of an individual to consent may be lost between the time of initially taking part in the research and the possible return of IF that might have benefits to their family.

(19) "it could be just the individual couldn't it? But could also be the family and in that case if someone had lost [capacity to] consent how would you handle the fact that you're giving information that could affect other members of the family."

Protective attitudes

A majority of REC members tended to countenance paternalistic practices for the reason of protecting the participant. These were evident across all aspects of the research spectrum, from what should or should not be included in the pre-consent information to what, if anything, should be returned to the participants in the form of IF.

Surprisingly, an overwhelming majority supported researchers overruling a participant's express wishes about receiving IF if there were potential clinical implications for the participant or their family.

There was a fear voiced by one REC member that a checklist of potential IF could be detrimental in the recruitment of participants.

(3) "if there is a checklist and you started putting down things that were really frightening like cancer you might actually scare people off completely"

Others suggested that an experienced researcher who understood the issues far better than the potential participants could guide them as to whether they should consent or not.

(8) "people who understand the science and are familiar with the problems in practice…..they are able to guide that person perhaps as to whether or not they should consent."

When it came to the return of IF and what should be returned, a number of REC members were concerned about the possible impact that negative information could have on participants. This paternalistic attitude appeared to be grounded in their own personal views on what they themselves would want to know.

(4) "the nurse in me says yes they should know but then the human side of me says that could lead to a whole barrel of problems that the patient or participant doesn't need to know about"

(17) "it's the best interest test that the researcher can have a discussion with the person's GP, if you see what we kind of build in rather than it landing on the doorstep in a letter."

However, there were dissenting opinions to this general feeling of protectionism towards participants. The comparison between the two viewpoints was very stark.

(12) "No I don't think everything should be revealed. I think it's too life shattering."

On the other side of the discussion was the view that research participants are actually afforded more protection than they require or even desire.

(19) "I think the truth of the matter is that most participants from my own experience is that they are happy to participate in these things, they are actually over protected in a sense and I shouldn't say this, I think very often for participants we are over protective so I think you shouldn't start saying we will only do it if it's this sort of disease or that disease."

Ethical considerations

As is to be expected with this subject matter, the majority of discussion focussed on many differing and often competing standpoints. Some ethical principles discussed frequently have been included in previous themes; however there were other issues discussed which deserve mention.

A number of REC members were very clear that research projects should not provide 'carte blanche' permission for researchers to engage in 'fishing expeditions' over and above the objectives of the study. This so called 'opportunistic screening' of participants was considered unethical and potentially harmful.

(23) "I think no, it has to be. I don't think these massive blanket permissions can be given, I think they have to stick to what they have sought approval for. To start looking for other things I think opens all sorts of cans of worms for them as well as obviously the patient as well too."

There was also a concern that participants needed to fully understand the implications of any IF they may be presented with. This referred to a wider issue with public education and understanding of genetics, as well as the evaluation of risk. There was concern that participants may make life changing decisions based on results that were uncertain.

(4) "I mean, if you have somebody with a BRCA2 gene, the cancer gene. There is a possibility to go ahead and have a mastectomy or something but that may or may not cause you untold misery for the rest of your life for something that you don't know."

Despite the previously mentioned majority support for overruling participant consent if the condition was serious, there were REC members who maintained that participant autonomy should always be respected, regardless of the implications for them or their family members.

(6) "That's hard to do because they consented to that being blinded. There is no consent to unblind it so you are caught there."

Rights of participants

The rights of the individual research participant formed a large proportion of the discussion by REC members about their views on IF return. Those rights were many, varied and often conflicting, from the right to know (or not) discussed earlier, the right to good health, the right to autonomy, freedom from coercion either by researchers or by family members, to the right not to be harmed by researchers returning difficult information.

Some believed the choices currently offered compromised the integrity of the consent provided.

(21) "I wouldn't wish the person whose DNA or genetics is being tested to be in some sort of moral blackmail because if they don't accept, don't wish to hear the results themselves it means that they leave the rest of their family blinded."

Others believed that severity of the condition should drive decisions by the researcher as to what IF to return depending on the potential practical impacts on a participant's life.

(9) "I think it depends on the severity, if it is something that is not going to affect life insurance or driving, or anything like that I don't think it matters but if it is going to affect them then generally I think they ought to be informed."

Some were very clear that researchers had to be honest with the pre-consent information and couldn't mislead participants about what they were agreeing to.

(10) You couldn't tell someone this is totally anonymised but actually incidentally we have found something nasty so we are going to find out who you are. You can't do that one."

Participant risk

An extremely pertinent issue to consider when engaging in any form of research is achieving full understanding of the potential risks to participants. Consequently, strategies must be put in place to mitigate this risk and also to manage any harm that may arise. REC members, as is to be expected, were acutely aware of the need to protect patients as well as acknowledging the complex and frequently individualised situations that genome-wide investigations may present. For this reason some were concerned at any attempt to suggest a standardised approach for IF return.

(8) "I think these are OK a difficult path I think that the whole purpose of the protection surrounding genetic research for participants are to the effect that those protections are concerned with the individual, every case is different and therefore if you have a blanket document of any sort you may be getting away from and I think that might be dangerous."

There was also the important observation that such information could not simply be presented to participants in isolation and that support in the form of genetic counselling, referrals for clinical testing and other medical assistance was key in a decision regarding IF return.

(18) "I think that is potentially really damaging to give people information without any support".

Personal opinion or those of the REC

There was a common thread running across the interviews that it was very difficult to discern what was the personal opinion of each REC member and what was their representation of their REC committee's position on such questions. Sometimes there were clues that REC members were giving their opinion with comments such as:

(19) "I shouldn't say this"

(4) "the nurse in me says yes they should know but then the human side of me says"

Discussion

The concept of obtaining informed consent from research participants has been enshrined in scientific practice since the Nuremberg code and Declaration of Geneva [19,20] were drawn up in response to the experimentation on humans in concentration camps during World War II. With the adoption of the Declaration of Helsinki [21], these ethical principles have been commonplace in research for over 50 years.

Due to the original reasoning for the establishment of such guidance, these issues have always been at the forefront of discussions surrounding genetic research. In an era of fast-moving technological advances allowing researchers to examine large swathes of genomic information cost-effectively (as opposed to relying on a more focussed gene-by-gene approach), the challenges of ensuring informed consent from participants have evolved. Issues include the uncertainty surrounding what is being tested, the open consent model for future testing and how to manage incidental findings.

Obtaining valid consent

REC members in the current study were aware that it was not sufficient for a participant to consent to take part in research, but all efforts should be made to ensure that the consent provided has

sufficient validity to reduce the need for interpretation and difficult decision making by researchers. There were concerns that participants could not be provided with sufficient information or consideration time to allow a fully informed decision regarding IF return. There was also concern that the ramifications for other family members may place significant burden, perhaps coercion on participants to make a particular decision and that this undermines the validity of the consent provided.

One of the problems of ensuring voluntary consent is the blurring of boundaries between research and the clinic [22]. Increasingly, genome-wide research studies are being carried out in a clinical setting and this has implications for consent. There is a danger that patients are not aware of having been through a consent procedure, despite having a good understanding of the study, if recruited by clinicians, or may confuse their previous research participation as being part of clinical care [23,24]. Healthcare professionals working in clinical genetics have discussed the importance of actively separating out their roles as clinicians and researchers to avoid potential conflicts of interest [25].

Where consent is sought, it is important that all participants taking part in research involving genome-wide technologies have the capacity to consent to such a study. The question of capacity is complicated by the fact that a participant's capacity can be subject to temporal and situational variations.

The idea of information overload acting as a barrier to informed consent in genetic testing has been previously described [26] and was raised as an issue in this study. For example, in the clinical sphere the idea of vulnerability in couples seeking IVF has been discussed [27]. The authors suggested that having difficult experiences and perhaps wanting a child 'at all costs', then providing all the relevant information for them to make well-informed decisions about complex tests may not be feasible. They further suggested it may not even be an acceptable goal to overload such patients with technical details and the uncertainties involved.

The difficulty of addressing the complex issues involved in whole-genome sequencing and communicating this to patients and participants without overloading them, which would counter the aims of obtaining consent, has been described as possibly prohibitively expensive and arduous [28]. Alternative models of consent have been proposed for genetic technologies. The traditional ideal of explicit and specific consent in a genomic testing context has been challenged by Manson and O'Neill, who place a higher emphasis on the process of information communication itself [29]. This would allow for tailoring of the level of information dependant on the ability of individual participants to receive it. In a screening context, the idea of a more 'generic consent' has been proposed and described to avoid the pre-test counselling process from becoming pointless and counterproductive [30,31]. These generic consent approaches allow patients or participants the autonomy to decide which categories of information from genome-wide tests they may (or may not) wish to receive [32]. This has evolved into the model of 'binning' or grouping different types in incidentally discovered genetic information according to severity, clinical utility and validity [33]. Inevitably though, any suggestion of binning will lead to further questions surrounding: who is best placed to decide the relative merits; the importance of different types of genetic information; and is clinical utility the only matter of importance for research participants? Some of the issues have been discussed in the context of the $1000 dollar genome [34].

As is to be expected from a sample of ethics committee members, the overwhelming majority of discussions centred on protecting the potential research participant. This is, after all, the primary purpose of such committees. A number of REC members believed there were things that participants didn't need to know or decisions where they shouldn't be afforded autonomy. These findings could further undermine the informed consent process currently employed. If a participant is not availed of all necessary information required to make a choice or, having come to a decision, their autonomy is not respected, then attitudes towards participating in research could be negatively affected.

Overruling consent

One of the most noteworthy findings in the current study is the observation that a large majority of REC members supported overruling the express wishes of participants made during the consent process if the IF had serious implications for the participant and/or their families. This was a surprising finding and it is hard to conceive that if a researcher approached a REC with a protocol detailing such a strategy it would be accepted without challenge. The arguments against respecting participant autonomy were strong and mainly concerned with a duty of care to protect the health of the participant and their family, a duty that was felt to be even more compelling if the researcher was also a clinician. However, despite the strength of these arguments, it is clear that a consent process in which IF are discussed, and in which a specific question regarding disclosure is included with the intention of overruling the participant's wishes should the circumstances demand, is not fit for purpose. Though such a precedent may exist, we were unable to find any comparable example where consent was overruled after it had been obtained from an individual with capacity, having presented all the relevant information, and having discussed and specifically asked about wish for follow-up.

Implications for practice

There are a number of issues which emerge from the responses received from REC members during the current study. The difference in time taken to consider and answer the questions could either point to certain REC members being so sure of the answers that they appear self-evident and require no discussion, or that certain REC members better understood the potential ramifications of the posed questions based on a more advanced level of genetic knowledge. Another issue is the difficulty of assuming that any opinions given are representative of the wider REC community, rather than merely the individuals' personal perspective. This is a major reason why we recruited both expert and lay members as opposed to just chairpersons, as in recent IRB research into IF [35]. It is reasonable to assume that in this type of interview setting, participants would give personal opinions. In fact, a strength of RECs is the multi-background composition of individual members facilitating such diverse opinions. However there are ramifications, one of which is that, as previously described, one REC member's view of what is or is not ethical may be in discordance with the wider committee [36]. The context of that study was the triage procedures used to determine which studies required full REC consideration and which contained no significant ethical issues.

The relevance to the current study is the observation that individual REC committees had, at best, one individual with an advanced knowledge of genetics and genomic technologies but that many committees had no such members. This required seeking advice from outside advisors, which means that potentially the decisions regarding

the ethical appropriateness of complex genomic testing protocols may have primarily rested at the hands of one individual, often not even a member of the REC themselves. Given the previously described disparities between individual and full committee opinion on ethical issues in far simpler studies than those discussed here, this is an observation worthy of consideration. Perhaps there is an opportunity for the generation of specialist REC committees to consider such applications. This could build on the existing framework of the gene therapy advisory committee, which has already been incorporated into the health research authority to consider clinical trials involving gene therapy. It also seems that, despite the requirement for expert (medical professionals or researchers) and lay members, there is no formal requirement for members with significant ethics experience. Whilst it might be difficult to incorporate an ethicist into every individual REC, much like the availability of a bank of scientific officers suggested by the Warner report there could be a centralised bank of ethicists available to give specific advice and guidance. However, it should be mentioned that despite the Warner report recommending this bank of scientific officers, there was no reference to such a service or resource by any of the participants in the current study.

Strengths and Limitations

While this study took place in one national setting, we took care to recruit REC members from multiple committees and with a range of backgrounds and expertise. The data collection was undertaken by one person, to maximise consistency and the data analysis was performed by three researchers, to ensure rigour. However, further studies would be needed in other national settings to confirm or refute the findings.

Conclusion

Caution must be exercised to avoid over-generalisation from an individual study. However, we have shown that members of numerous REC committees across the UK are aware of the possibility of genetic and genomic incidental findings in a research setting, despite to date having little first-hand experience. We have also shown that there is no consensus on the way in which to present information prior to consent, or which mode of consent form is most favourable. We have also described how REC members have difficulty in balancing the rights of individual participants, their families and the researchers and clinicians involved in the study when it comes to the return of IF. Further studies are needed to provide appropriate and timely guidance to REC committees in how to deal with such questions in an era of genome-wide testing to ensure consistency of decision making across the UK and optimal protection for participants.

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