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An ethical review of the use of functional MRI and DNA analysis in birth cohort studies

Martin Richards

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**An ethical review of the use of
functional MRI and DNA analysis in
birth cohort studies**

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August 2011

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Introduction

This review concerns two areas of research practice that raise significant ethical issues and that have been the subject of much controversy and debate. The first part concerns magnetic resonance imaging (MRI) and, in particular, the fraught issue of feedback of incidental findings to research participants. The second part concerns the analysis of research participants' DNA. The review is based on relevant ethics, socio-legal research and clinical literature. It is guided, particularly, by two principles of research ethics. The first is respect for persons, which emphasises the research participant as an autonomous individual capable of deliberation about their own goals and actions. Respecting autonomy is to give due weight to the autonomous person's considered opinions and choices while refraining from obstructing their actions unless these are clearly detrimental. The second is the duty of care researchers hold with respect to their research participants. At the same time research may be regarded as a public good and should not be impeded or inhibited without good reason of concern for the wellbeing and protection of research volunteers.

The context for this review was a funded network, set up to discuss the potential for future inter-disciplinary research on genetic, social and neuropsychological influences on individual differences in impulsivity and memory. The review used a lifecourse approach, which included a pilot study on conducting more detailed neuropsychological assessments with a small subgroup of members of the 1958 British birth cohort study (also known as the National Child Development Study or NCDS). This was funded under the joint research councils' 'Understanding Individual Behaviour Exploratory Network' programme. Particular attention is therefore paid to the ethics of functional MRI (fMRI) and DNA analysis in birth cohort studies, although much of the discussion here could be applied to fMRI and DNA analysis in any non-clinical research study.

Part I

The use of functional magnetic resonance imaging in research studies

MRI was originally developed as an investigative tool in clinical medicine but now is increasingly used in a variety of research studies. In neuroscience, fMRIs of the brain are widely used to gain information about brain function and individual differences (Logothetis, 2008). While the process of imaging itself poses minimal risks to research volunteers, these techniques may reveal pathological conditions of which the "healthy" research participant is unaware. Such incidental or unexpected findings are relatively common (Morris et. al., 2009) and have important implications for the process of informed consent, the potential need for clinical analysis of images and the manner and pathways for informing participants, and for the participants themselves, with possible serious implications for their health and wellbeing (perhaps including their employment and access to health and life insurance). There is variation in how such incidental findings are handled in research settings and

guidelines that do exist are incomplete and inconsistent (Booth, et. al., 2010A). Practice and opinion differ over matters such as the information that should be given to research participants before consent is obtained, what incidental findings should be fed back, whether scanning should be enhanced to aid identification of pathology, who should review the images, how feedback should be arranged and who should be told, or indeed, whether any such feedback should be given to research participants.

A recent review of the UK legal and ethical guidance on incidental research findings in imaging research found most were consistent with

The principle that research volunteers should be informed of how their research images will be managed, that measures should be in place for identifying and acting on incidental findings, and that information should be disclosed to the subject and their responsible physician in a timely, sensitive and appropriate manner (Booth, et. al., 2010A).

Those principles are also the conclusion of this review. However, I will go beyond these by setting out more detailed guidelines for practice that follow from the ethics analysis. We may note here that the Booth et. al. (2010A) review of practice and guidelines concerning the management of incidental findings in research also concluded that guidance is “inconsistent, limited and does not address the interest of [research] volunteers”. A wider consideration of those latter interests informs this current review.

fMRI imaging

The process of MRI involves the patient or research participant lying still in a very confined and noisy space for a significant length of time (up to an hour or more). This may engender feelings of claustrophobia and anxiety. The magnetic field can cause movements of ferro magnetic implants and may interfere with the operation of pacemakers. In clinical practice the main source of morbidity has been associated with the risk of injury from metallic projectiles, which have resulted in at least one death (Colletti, 2004; Detre, 2008). However, this risk is easily controlled by procedures that ensure no ferrous objects are brought into the magnet room. Current NHS protocols for clinical scanning ensure that the procedures are very low risk.

Most healthy research volunteers, especially younger ones, are unlikely to have had previous experience of being scanned. When consent is being sought for participation in research studies, all potential research participants should be given information about what the scanning process involves and its potential minimal risks.

Incidental findings in research studies

An incidental finding may be defined as a previously undetected abnormality of potential clinical relevance that is unexpectedly discovered and is unrelated to the purpose of the imaging. In a research setting the MRI protocol is designed for a specific research question, in contrast to clinical protocols developed for particular

clinical problems. The prevalence of detected incidental findings will depend on the resolution and image sequences in the MRI protocol (including the use of contrast), the training and experience of the reader, the use of a pre-specified analysis protocol, the post processing of the image, and of course on characteristics of the population being scanned. Detection rates are likely to be considerably lower than the “true” prevalence based (for example) on data from autopsies (van der Lugt, 2009). A broad indication of the possible prevalence in research studies is provided by a recent meta-analysis based on 16 studies involving almost 20,000 participants (Morris et. al., 2009). This found an overall prevalence of incidental findings of 2.7 per cent, with the number of asymptomatic people needed to scan to detect any incidental finding being 37. This was based on participants without neurological symptoms with incidental brain findings of potentially symptomatic or treatable abnormalities (excluding markers of cerebrovascular disease)¹. The prevalence of neoplastic brain findings (0.7 per cent) increased with age, as did white matter hyperintensities and silent brain infarcts (makers of cerebrovascular disease). The detection of incidental findings (excluding makers of cerebrovascular disease) was higher in studies using at least one high resolution sequence than in those using standard resolution, a common practice in research brain imaging. The detection of incidental findings was not higher, according to this review, if neuroradiologists interpreted the images.

Feedback

The ethical argument for feedback of incidental findings to research participants is based on the duty of care that researchers have toward those participating in their studies. While a clear and well-established duty of care exists for doctors in relation to patients, it is less well defined in research relationships (e.g. Miller, Mello and Joffe, 2008). It may also be held to vary across research settings related to such considerations as the invasiveness of the research, the extent of data being collected and the duration of the research relationship. While doctors are required to act in the best interests of their patients, a researcher is expected to exercise reasonable care towards their participants and to respect them as persons. On this basis there is a broad consensus, reflected in most guidelines, that researchers should provide their research participants with information generated through research procedures that may be expected to be beneficial to participants and their health². Thus there is a

¹ These white matter hyperintensities, silent brain infarcts or Lacune and brain microbleeds are incidental findings. However this study did not focus on them because of their known increasing prevalence with age, their largely unknown role in causing symptoms and the current uncertainty about whether or not to institute primary prevention after detection (Morris et. al., 2009; see also Cordonnier et. al., 2007; Vermeer et. al., 2007). A recent systematic review (Debrette and Markus, 2010) found white matter hyperintensities predict increased risk of stroke, dementia and death suggesting that they are clinically relevant even when found incidentally on brain imaging (Wallin and Fladby, 2010).

² It has been argued that there may also be a legal obligation based on the common law duty of care and Article 2 of the European Convention on Human Rights for researchers to provide feedback concerning serious treatable disease (Johnston and Kaye, 2004). See also Wolf, Paradise and Caga-anan (2008) for a discussion of the situation in the USA. However, a recent survey in the UK suggested that a significant minority of centres never feed back incidental findings (Booth et. al., 2010B).

clear case for feeding back an incidental finding of a treatable condition so that a research participant, who has opted to receive such feedback, may experience the benefit of earlier and perhaps more effective treatment than might have been the case if diagnosis had occurred at a later time following the development of overt symptoms. An incidental finding could also indicate that preventative action is required to avoid the development of a serious condition.

While a duty of care can mean that researchers should feed back any potentially beneficial information they come across in pursuing their research protocol, there is no duty to seek out such information beyond the research protocol. It has been suggested that clinical standard scans should be added to the protocol in MRI research using relatively low resolution scans, as clinical scans are more likely to reveal incidental findings. While we might regard this as a researcher simply doing the participant a (potential) favour³, there can be no requirement for researchers to adopt a clinical standard of scanning for a research study. That would both redirect the purpose of the study and move beyond researchers' duty of care. However, low resolution scans (often used in fMRI studies) may make the interpretation of potential incidental findings difficult. Arguments have been made to include higher grade scans in research studies, so that incidental findings may be disambiguated and potential false positives reduced. However, as bedevils this whole field, we lack systematic evidence that might indicate whether or not this would improve the "quality" of feedback participants might receive.

In research studies it is important that participants do not regard the research procedures as health checks (the therapeutic misconception) because they could then be falsely reassured that all is well if they do not receive any feedback, or believe that feedback will indicate all potential problems. This is especially important when using research procedures (like MRIs) that are similar to clinical assessments and that participants may assume are also clinical assessments. In a USA study of control subjects who had participated in neuroimaging studies for research purposes, over half of them said they expected research scans to detect abnormalities if they existed, regardless of what had been said in the information given them in the consent process (Kirschen, Jaworska and Illes, 2006). There is also some anecdotal evidence that some people who suspect they have brain abnormalities may go out of their way to volunteer for MRI studies as they see this as a way of getting a diagnosis. It has been suggested this may be why there are "high" prevalence rates for incidental findings in some studies. However there is little basis for judging what a "high" rate might be.

There is little evidence about what leads people to volunteer or decline invitations to join MRI research studies or about the typical characteristics of volunteers and decliners.

A small pilot study (N = 45) has been carried out with members of the 1958 birth cohort study, the National Child Development Study (Brown and Knight, 2010). The

³ Assuming, of course, that the feedback of any additional incidental finding that might be observed was beneficial to the participant.

majority (95 per cent) said they would be willing to take part in an fMRI study. Sixteen per cent of these had been previously scanned for clinical reasons. While 43 per cent of the participants said they would agree to take part regardless of whether or not they received feedback, 41 per cent said they would only do so if they got feedback on all potential problems and 11 per cent said they would do so if they received feedback on potential problems considered to be serious and treatable. Stated motives for taking part in such a study included contributing to important research, loyalty to the cohort study, and the possible opportunity to benefit from early detection of problems or the reassurance a scan might provide that all was well.

What to feed back

The intention in providing feedback is to “inform participants of incidental findings [that are] believed may have significant clinical importance, which they may derive net benefit from knowing” (Hoggard et. al., 2009, see also, Illes et. al., 2006; 2008). But, as many have pointed out, the significance of incidental findings may be unknown or controversial. Further, we should note that judgements about what is clinically significant are based solely on the examination of a scan without a wider clinical examination or knowledge of the participant’s medical history. For example, Detre (2008) notes that “the presence of a few subcortical white matter hyperintensities is typically insignificant in a subject with no history of neurological complaints, but may strongly support a diagnosis of multiple sclerosis in a patient with a clear history of transient neurological deficits”. He goes on to say that the “risks associated with an incidental finding may also vary from individual to individual. One subject may accept the presence of a small aneurysm or tumour and decide to undergo period follow-up scanning”, while others may seek risky interventions.

Ethically, two points follow from this. First, not all those who receive feedback will receive the intended net benefit. For some, because of engendered anxiety, unnecessary or inappropriate treatment, or risks associated with treatments, there will be a net disbenefit (Royal and Petersen, 2008; Wolf, et. al., 2008). There may also be adverse consequences for medical and life insurance or employment (e.g. Anon, 2008)⁴.

Secondly, the decision to inform participants is a clinical judgement that should be based on the best available evidence. Who then should be making this judgement? Should this be whoever analyses the research scans, or should there be a review by a neuroradiology specialist? Policies and practice varies. While radiographers and research scanners may (or may not) be very experienced, neuroradiologists are an

⁴ While we have research on the prevalence of incidental findings, we lack systematic studies of the outcomes of providing feedback. The aim of feedback is for net benefit and we may assume this is the usual outcome. But we know that for some it can be a disaster (e.g. Anon, 2008). But without empirical evidence we cannot claim practice is evidence based – nor is there a proper basis to adequately inform research participants about the possible outcomes of their volunteering. It might be suggested that those who undertake research involving scanning should, at least, systematically record health outcomes for those who receive feedback to determine what benefits or disbenefits may follow. But ideally rather more robust research methodologies are required to determine effects of offering or not offering feedback.

expensive and scarce resource. However, a decision about feedback is essentially a clinical decision. A two-step process has been suggested for some research situations, including biobanks (where numbers of participants may greatly exceed any current research studies); a radiographer refers suspicious scans and a radiologist evaluates these and decides whether feedback is appropriate (Hewitt, et. al., 2010). Those who might want to defend evaluation by radiographers or researchers might point to Morris et. al. (2009), who found that the prevalence of incidental findings was not significantly higher in studies where evaluations were carried out by neuroradiologists rather than radiographers (see also, Brown and Hasso, 2008; Ulmer et. al., 2009). Of course the issue is a matter of the appropriateness of feedback, not the number of incidental findings. However we lack the evidence on outcomes of providing feedback needed to settle the matter.

Typical fMRI research images alone are not a suitable basis for good clinical judgements. While a full clinical MRI scan may not be appropriate in a research setting, “good enough” imaging may be required: the minimum imaging that can reduce the number of equivocal findings that could lead to unnecessary investigation, anxiety, etc. (Hoggard et. al., 2009; Booth et. al., 2010A).

There is also an issue of practicality and resources here. A recent meeting of representatives from UK research imaging centres, professional bodies and organisations involved with imaging research reached the following conclusion:

While accepting that having a qualified radiologist review all research images, with additional diagnostic images obtained when necessary, would be the most sensitive and specific method for identifying incidental findings, there would be serious practical implications were this to be implemented universally. There are currently too few radiologists in the UK to provide such a service. Many research imaging sequences do not include diagnostic images and, indeed, the addition of these sequences might reduce subject tolerance and impair research image quality. Enhancing all images to this standard would add very significantly to research costs, would risk increasing the frequency of incidental findings without clear benefit and might hinder or delay the results of much-needed publically funded research⁵.

Thus far in discussions the assumption has been that the aim of feedback is to give participants only information that is likely to be beneficial to them. However, there is evidence that some participants would wish to know everything that is found. A USA study of healthy control subjects who had had experience of participating in neuroimaging research (in medical and non-medical settings) found that at least 90 per cent of the group would want to be informed of incidental findings regardless of whether they were “benign; malignant, but curable; malignant, not curable; or a life

⁵ Ethical Management of Research Imaging. Report of Meeting of Research Imaging Centres and Organisations Involved in Research Imaging held on 1 July 2010. Wellcome Trust, London. Draft 20110314 V5, 14 March 2011. Following this meeting new guidance for RECs was produced, which is currently (March 2011) being considered by the National Research Ethics Advisory Panel. Incidental findings in imaging research: a framework for considering ethical issues (Draft, March 2011).

threatening emergency” (Kirshen, Jaworska and Illes, 2006). This has led to the suggestion that participants be offered a choice of which incidental findings should be fed back. They may choose either feedback only in situations where a strong net benefit may be expected (a condition likely to be life threatening or likely to be grave that can be avoided or ameliorated), or feedback of such conditions as well as those offering a possible net benefit (a condition that is likely to be grave or serious but that cannot be avoided or ameliorated) (see also Booth et. al., 2010A). Clearly, if such a choice was offered it would be imperative that participants understood the implications of their choice. However, from the point of view of those reviewing scans, knowing a participant’s preference may help clarify more difficult decisions about when to provide feedback. An implication of the choice would be that those opting for the broader feedback option would be more likely to receive feedback that led to disbenefits, while those who chose the strong net benefit only option could miss out on more uncertain feedback that may have been beneficial. For those who want to know everything, we should presume information about a benign or incurable condition is a benefit.

The practicalities of offering such a choice to those who wish to receive feedback are formidable. Perhaps the more important conclusion from this research is not that we should attempt to set up two-track systems of feedback, but rather that a large majority of research participants expressed a preference to receive feedback of all incidental findings – benign, malignant, curable and incurable. If these research findings were confirmed for UK research participants, the work would have implications for how a significant incidental finding is defined.

There are also those who would not wish to have feedback in any circumstances, being well aware of the potential disbenefits. However offering a no feedback option is not general practice at present and there are those who believe there are medico-legal imperatives to provide feedback. There are also those who argue that such an option should be conditional, and feedback should be provided to all participants in situations where it is clearly beneficial, where there are potential third party risks, or both.

While researchers’ a duty of care is the basis of offering potentially beneficial feedback to participants, it would not seem to follow that such a duty of care should lead to a situation where a researcher is bound to provide feedback when an informed participant has expressly indicated that they do not wish to receive it. It can be argued that we should respect a participant’s decision not to receive feedback. In addition, we should not deny a person the opportunity to contribute to research by requiring all participants to receive whatever feedback is judged to be appropriate by the researcher. It is important to acknowledge here that in brain scanning, we have very little evidence about the benefits and disbenefits of receiving feedback of incidental findings. It is clear there can be both. Therefore we might expect that some informed participants may decide to forego potential benefits in order to avoid any disbenefits. While evidence suggests there are few such people, that fact in itself is not an argument for excluding such people from research.

However there is a very important caveat here. Regardless of any participant preferences about feedback of incidental findings or any conditions set out in the consent process, if during the course of scanning evidence comes to light that might reasonably be seen to indicate a life threatening emergency serious threat to third parties, it would be the duty of the researcher to act appropriately and such actions would certainly include informing the participant of the observations and their implications.

Feeding back

It may be appropriate for the scanner or the reviewing neuroradiologist to provide the feedback to the participant and to facilitate a referral for diagnosis and treatment. Otherwise, this could be done by another appropriately trained clinician. Clearly this is a task that should be entrusted to someone experienced in giving clinical bad news. Of course it would be the participant's decision to seek further investigation, diagnosis and to make treatment decisions. A question arises about the involvement of the participant's GP in this process. Some research groups record the name of a participant's GP before scanning takes place and then inform the GP if there is feedback. Others only inform the GP after getting explicit permission from the participant (Pickard and Gillard, 2005). Some centres will not scan individuals who do not agree to information being passed to their GP⁶.

The argument for involving the GP is that this may aid the participant in making decisions about further investigations and treatment and that it brings knowledge of the participant's medical history into the picture. However, there may be participants who do not wish to have their GPs involved (or to have incidental findings recorded in their medical records) and autonomy principles require consent to be given to pass information to anyone beyond the research team (a reviewing clinician or others who might be involved in informing the participant would be regarded as part of the research team, as should be made clear in the information a participant receives in the consent process).

Those who want to involve the GP without the explicit consent of the participant make two points in defending this breach of confidentiality. First, by reason of the incidental findings, some participants may not have the capacity to make appropriate decisions about their treatment and the GP can assist them in doing so. This raises a whole series of issues. However, this current review is made on the assumption that "healthy" volunteers for fMRI research will have the capacity to consent to take part in a research study and to make whatever decisions may be involved if feedback is given. It is, of course, possible (though very unlikely) that between a participant giving their consent to be scanned and the time when feedback is offered, someone may lose their capacity to consent. If this were to happen, the person should be excluded from the study and assisted to find appropriate medical care. In such a situation it might well be appropriate, and in the participant's interests, for the

⁶ There are centres that send a feedback letter to the GP and do not communicate directly with a participant. Such a practice could result in the GP letter being simply filed and no action taken on it.

researchers to inform whoever is providing that medical care about what the scan revealed. However, none of this would justify the routine disclosure of research information to a third party without the knowledge and consent of the research participant.

The second point concerns third party risks. This includes the unlikely scenario of, for example, the discovery of an epileptogenic tumour in the brain of a healthy, symptomless bus driver. If the GP is informed about what the scan has revealed, steps can be taken to remove the participant's driving licence. Do such possibilities justify informing a GP about feedback, in *all* cases, without seeking consent of the participants? I would suggest not. Researchers have some duty towards protecting third parties as well as their duties of care and confidentiality to the research participant. However, in the situation of discovery of evidence that the participant might be a danger to themselves and others, it would be for the researcher to take appropriate action, as I have already noted. This might well include informing the GP of the situation and could be justifiable whether or not the participant has given prior consent for this.

An important question related to duties and responsibilities arises when the participant becomes a patient and enters a doctor-patient relationship. This needs to be explicit in research protocols. A commonsense view would be that providing feedback to a participant, even when done by a clinician, does not create a doctor-patient relationship. Rather, this is a research participant being given information by a member of a research team. Only if and when the participant seeks medical advice does the participant become a patient.

Later analysis of data

In the context of a birth cohort study, fMRI data from a subset study (or the whole sample) could be made available for further analysis in subsequent research using cohort study data.

What if those later researchers came across incidental findings? Of course it is most likely that the incidental finding would be something already identified in the review of the scans carried out when they were first done. However it is possible that new incidental findings might be identified, perhaps because the scans are subjected to a new kind of analysis or because there is new knowledge of the significance of a previously unrecognised biomarker. So should scans be subjected to a new clinical review in light of new knowledge from further research analysis? Of course, this would now be historical data. Progressive conditions may have become manifest or the opportunity for adopting risk reducing strategies may have already been lost. Given that a new clinical review of the scans is relatively unlikely to disclose much by way of new information that would be beneficial to the participant, it would seem to be going beyond the reasonable expectations of a duty of care to undertake a further review. However, participants should be made aware if later research analysis of their data may be undertaken and that there will be no feedback.

There is a wider issue here, which has been discussed in ethics literature particularly in relation to genetic information: if advances in knowledge could reveal new incidental findings of significance from stored data, should researchers review that data so new incidental findings could be fed back to participants? Earlier in this paper I suggested that researchers' duty of care does not mean that they should couple their research investigations with additional clinical scans and assessments beyond the research protocol. The same argument would imply that a re-examination of stored MRI data simply to search for potential incidental findings to feed back to participants is not justified.

It may well be that the consideration of later analysis of scans is not necessary. Given the very large amount of information in a scan, it is not uncommon that in longitudinal studies only some analysis of a scan would be stored. In such data the discovery of "new" incidental findings in later analysis is very unlikely.

The Data Protection Act 1998

Under the Data Protection Act 1998 there is no obligation to provide research participants with information about incidental findings, but there might be if a participant specifically requests disclosure. There are research exemptions in the Act, but these may not apply in situations where there is the possibility of incidental findings being fed back as decisions are being made about information relating to particular individuals (English, et. al., 2007). So if an individual's data is being evaluated, there could be a legal duty for researchers to provide information on request to a participant. If this interpretation of the law is correct (and it does not seem to have been tested in practice), it would seem that any participant (whether or not they have been given feedback) could request access to their scans, if these have been reviewed, and researchers would be required to provide these⁷.

Current guidance

I have already referred to Booth et. al.'s (2010A) review of existing guidance and their conclusion about its weaknesses and inconsistency. However, in the context of this review there are two guidance notes that are directly relevant and deserve mention.

The National Research Ethics Service (2007)⁸ provides guidance on informed consent:

"The subject must be adequately informed ... of the possible disadvantages and risks of taking part [in research] ... any risks, discomforts or inconvenience should be briefly outlined ... [possible benefits should also be outlined] ... The potential participant should be told what would happen if other conditions were

⁷ However, if a study offered a no feedback option to participants, those taking that option may not be able to seek feedback because their data would not necessarily have been subject to individual review and would therefore be covered by the research exemption.

⁸ I noted earlier that new guidance for ethics committees is currently under consideration by the National Research Ethics Advisory Panel.

discovered of which he or she was unaware ... the published literature should be consulted and material presented to likely participant groups to assess its value ... you should consider insurance issues and whether patients should be informed that their participation may affect insurance cover ...

You should explain if the participant's GP (or health care practitioner) needs to be notified of their participation, and seek consent. You should explain what information will be exchanged.

...it must be clear if the data is to be retained for use in future studies and whether further [ethics committee] approval will be sought ...”

[From Booth et. al., 2010A]

The Medical Devices Agency (2002) recommends disclosure when incidental findings are identified in all volunteers undergoing MRI, followed by appropriate onward clinical referral. It also recommends that all examinations of MRIs are reported by a radiologist.

Conclusions

This review suggests the following conclusions and implications for research protocols and the consent process.

- 1) Research studies should have a clear protocol for the identification and feedback of incidental findings indicating the pathways to be followed.
- 2) Incidental findings that are potentially clinically significant should be fed back to research participants who wish to receive feedback.
- 3) During the consent process potential participants should be made aware of the risks of the scanning process, the likelihood and nature of potential incidental findings and the process of their identification, feedback and the possible outcomes of receiving feedback. Potential participants could be offered the possibility of:
 - a) feedback of incidental findings where a strong net benefit to the participant may be expected
 - b) feedback of incidental findings that are of potential clinical significance or where a strong or possible net benefit may be expected
 - c) no feedback⁹.
- 4) For each of these possibilities, participants should be made aware of the benefits and disbenefits that may accrue. These, and the descriptions of the possible outcomes of receiving feedback, should be described in accessible language.
- 5) If scanning provides evidence suggesting a life-threatening emergency and/or serious threat to third parties, a researcher would need to take appropriate action regardless of the feedback preferences of a participant.

⁹ It should be noted that the option of no feedback is counter to the recommendations of the Medical Devices Agency (MDA) as summarised above. There are clearly some researchers, including collaborators on the project, who have the view that it is irresponsible not to follow the MDA's recommendations. However, for the reasons discussed above, I conclude that no feedback should be an option offered to potential research participants.

- 6) It is important that participants understand that the scan is being carried out to answer research questions and does not consist of a medical examination of the brain. It is not a substitute for the scans used in hospitals for medical diagnosis.
- 7) Feedback to participants under options a) and b) of recommendation three above would preferably be provided by a neuroradiologist or other appropriately trained clinician. A participant's GP would be informed of the feedback, if consent is given. The clinician offering feedback would facilitate the participant's access to appropriate diagnostic assessments and treatment (if appropriate).

The recent review by Booth et. al. (2010A) includes good practice guidelines that are broadly consistent with what has been suggested in this review. Regarding the duty of care, the standards set in current guidelines are the standards against which liability claims are likely to be assessed (together with what might be the reasonable expectations of the participant) in a situation where a participant had been harmed. As mentioned earlier, new advice is being prepared for ethics committees who are then unlikely to give favourable decisions for projects where protocols do not meet the expectations this advice embodies.

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Part II

Genetic and genomic research in cohort studies

The analysis of DNA has a number of features that need consideration in any research protocol because of their potential implications (e.g. Richards, 2001).

1) Identifiability

It is possible to identify a person through comparisons of anonymised DNA samples or of some genetic information derived from DNA analysis, with those from a named person¹⁰. It is also possible to show, for example, whether a particular individual's DNA is included in complex genomic DNA mixtures (Homer, et. al., 2008; see also P³G, Church, Heeney et. al., 2009 for responses to this threat). These cases could breach confidentiality. Of course, research involving DNA collection and analysis is not unique in this way, as social and demographic data could be used in a similar fashion to identify research participants. As is general in research practice, steps should be taken to ensure confidentiality of research data and reduce possibilities of identification of research participants. It is important not to make claims to research participants that data has been rendered 'non-identifiable' when this is not in fact the case.

2) Disease

DNA can be analysed to reveal mutations of genes associated with Mendelian¹¹ (single gene) diseases. Such genetic analysis is used clinically for diagnosis, prediction of late onset diseases, identification of carriers and calculations of risks of transmission to children. Because these are inherited diseases that run in families, the identification of mutations associated with a Mendelian disease may have implications for blood relatives. While most Mendelian diseases are rare, some common diseases have subsets of Mendelian diseases (e.g. breast and other cancers associated with mutations of the BRCA1 and 2 genes, which account for perhaps 5 per cent of breast cancer cases).

Most Mendelian diseases are very rare. For example, in the UK about one in twenty of the population are carriers for the most common Mendelian disease, cystic fibrosis (1 in 4 children of two carriers will develop the disease). The rarity of these diseases means that it is unlikely that work related to them would be carried out in birth cohort studies. However, there is increasing evidence that some very rare (mutations) together with other variants (such as copy number variants) may be associated with common diseases and attributes that could be of interest to researchers. In addition, research approaches involving whole-genome sequencing (sequencing the entire DNA of individuals to personal genome sequences) are rapidly becoming more

¹⁰ The exception here is monozygotic twins. These share most of their genomes and they are probably only distinguishable through full sequencing of their DNA. Currently employed paternity or forensic DNA testing techniques will not distinguish them.

¹¹ See glossary for further explanation of this and other terms.

common¹². This technology produces a huge amount of data. The interpretation of some of this could be of clinical significance for research participants.

Common genetic variants (single nucleotide polymorphisms – SNPs)¹³ may be associated with common diseases. While sequencing of DNA can also reveal very rare variants (essentially Mendelian diseases) and structural features, genome wide association (GWA) studies¹⁴ have established associations between SNPs and common diseases and personal characteristics. While SNP associations may be important in understanding disease processes, in most cases these account for a limited proportion of the disease heritability only, and at best are very poor predictors of disease. For a few diseases of later life (e.g. Alzheimer's disease) SNPs may be rather more predictive. SNPs may also indicate individual responses to therapeutic drugs. In a few circumstances, SNPs related to certain diseases, together with other information, may have some clinical utility, however limited (Ashley et. al., 2010). SNP-based disease predictions are commercially offered in "personal genome scans" (e.g. Richards, 2010). Robust utility in clinical prediction or management is yet to be demonstrated for SNP-based predictions, except in the case of some drug responses.

In studies that reveal gene mutation associated with Mendelian disease or other clinically significant results, the issue of feedback to participants will arise. Where SNPs are involved, because associations with disease (or traits of significance) are generally weak, there is little case for the consideration of feedback of such information to research participants. However, this position would change if robust clinical utility were to be demonstrated. SNPs can also be used to predict responses to some widely used therapeutic drugs. This is information that could be of benefit to some research participants and so issues of feedback may arise if this information is generated in a research study.

3) Abilities and attributes

GWA studies have been carried out with a wide range of phenotypic characteristics including various abilities and attributes, and have established some associations with SNPs. Of course, cohort studies typically collect much information directly about such traits, for instance in the form of psychological test scores. If studies produce information that is to be of benefit to research participants, there is an issue of feedback. There are attributes that can be reliably predicted with SNPs (e.g. eye and hair colour), however, there would seem no benefit in feeding back such information to research participants. However, at present there do not seem to be examples of SNPs strongly associated with characteristics that might benefit participants to know and that are likely to be examined in cohort studies. But this situation may change with continuing research.

¹² They are also becoming increasingly affordable. Currently a bulk order of 1000 genomes might be priced as low as \$5500 (Aldhous, 2011).

¹³ See Glossary for further explanation of these terms.

¹⁴ As above.

4) Relationships

As we have already noted, a diagnosis of a Mendelian disease in an individual may have implications for other family members who potentially carry the same disease-associated mutations. Beyond this, DNA analysis can reveal the presence or absence of biological relationship of family members. Thus, for example, when DNA from parents and children is being analysed it can indicate 'non-paternity', that is to say that a child is not biologically related to the (social) father, so may have been conceived through sperm donation or through an extra marital relationship. This will be information which may or may not be known to the family members concerned. Care should be taken to avoid situations where the feedback of results or genetic information that could reveal to participants the nature of genetic relationships between family members.

Feedback

There are already population studies in which feedback of genetic information and its implications has occurred. Developments in technology and research are likely to mean that much more information, which could be clinically significant, will be generated in research studies. In broad terms the principles and procedures for feedback of genetic information would follow those outlined for incidental findings in fMRI scanning.

There is at least one example of a population study that revealed genetic information of potential benefit to participants where this has then been fed back to participants. The example is a study of the prevalence and penetrance of BRCA1 and BRCA2 gene mutations in a population of women diagnosed with breast cancer (Anglian Breast Cancer Study Group, 2000). BRCA1 and BRCA2 are names of genes popularly referred to as "breast cancer genes". These are genes which have mutations associated with the development of breast and other cancers. Or one might say a small proportion of breast cancer cases are Mendelian diseases associated with a raised risk from BRCA1 or BRCA2 gene mutations. This study set out to establish what proportion of a population of women, all of whom had had breast cancer, carried mutations of the BRCA1 or BRCA2 genes. In the study, those who had requested feedback and who were found to have a BRCA1 or BRCA2 mutation were told that something of significance for them and their family had been discovered and they were referred to a genetic clinic for genetic counselling and clinical testing. There is an important issue here: the methods used to identify gene mutations in a research study may not be clinically valid test procedures. So clinical testing is required for those who are thought likely, on research evidence, to carry gene mutations. The protocols are similar to those used when incidental findings are fed back in an fMRI study and the person then proceeds to seek a clinical diagnosis. In the Anglian Breast Cancer (ABC) study, some of those receiving or not receiving feedback were subsequently subject to a further socio-ethical study. We should add that at the time of this study, clinical mutation testing for those at high risk of familial breast cancer was a clinical diagnostic procedure.

The women in the study, who had all had breast cancer (N = 1500), were offered the possibility of feedback if anything of significance for them and their family was found in the research analysis of their DNA. Ninety-three per cent of the women opted for feedback, if anything was found. BRCA1 and BRCA2 mutations were found in a very small proportion of the women. The women who had opted for feedback received a letter saying that something of significance had been found and they were referred to a genetic clinic for genetic counselling and mutation testing (to clinical standards). Subsequently these women typically took actions to reduce their continuing risk of developing breast cancer and in some cases passed relevant information to relatives. Some had no previous family history of breast cancer so, without the ABC study and feedback, they would have not have been aware of their familial risk of cancer – a risk that will, of course, continue after their diagnosis and treatment of a cancer.

However, as in the case of MRI incidental findings, feedback was not without its complications. In one case a woman, when tested in the clinic, was not found to have a BRCA mutation. She was left somewhat frustrated and annoyed, believing (on the basis of her family history) that she probably did have an inherited risk of cancer but thought this must be associated with a different gene yet to be identified. Things were even more difficult as, unknown to the research team, she had a sister who had also been enrolled in the ABC study. When the first woman received her letter with feedback, she told her sister (who had not had a letter) and both came to the genetic clinic. The sister was also found not to carry a BRCA mutation. These sisters were very critical of the study for giving them feedback when the researchers “could not have been sure” and for pointlessly sending them off to the genetic clinic¹⁵.

While this study may illustrate how genetic feedback can be offered, it is unusual in that a population that already has the disease of research interest were involved – and who might therefore be seen to have a particular interest in knowing whether or not their disease is familial. It is also very unusual in that the original research study was followed up with a second study that examined the consequences of offering feedback (though, for ethical reasons, the minority who declined feedback in the original study were not sampled in this follow up study).

Across a variety of research studies evidence is consistent that most participants want clinically significant results returned to them (Shalowitz and Miller, 2008). There is, for example, a survey of participants (N = 1857. 2/3 female, mean age 60 years) in a genetic cohort study of a Japanese population that found that most (90.8 per

¹⁵ This follow-up of research participants also found other criticisms of the ABC study. Many complained that they had never been told the “results” of the ABC study. This was not something they had been promised but many of them said that getting a description of the findings was something they wanted and felt they could reasonably expect in return for their time and donation of a blood sample, their family history and other data. As a result all participants in the ABC study were later sent a report of the study’s findings. Interestingly, many of those interviewed had no memory of giving consent to the study or being told how they had been recruited (via the Cancer Registry). Most thought that their GP or the Oncology Department would have given their names to the researchers – and were perfectly happy about that. Many said they knew it was a genetic study only because a family history had been taken – not because they remembered the description of the study given in the information sheet when they had given their consent to take part.

cent), but not all, participants wanted to be re-contacted with individual results if a particular problem was found related to a serious disease for which effective treatment were available. Those who were younger, former or current drinkers, and had at least one parent who had had cancer were more likely to want results. Those with at least one sibling with a medical history of cancer were less likely to want results (Matsui, Lie, Kita, et. al., 2008). A Dutch survey found that most citizens and patients would like to receive general information and information about gene mutations. A higher proportion wanted information about mutations than other general information about their health. A sample of researchers was less keen on giving feedback to their participants. For instance, a majority (60 per cent) of citizens and patients thought that researchers should inform participants about mutations even when the implications for health were unclear yet. But 95 per cent of researchers disagreed. Most researchers (74 per cent) thought participants should only have information about mutations associated with treatable or preventable diseases while only 34 per cent of participants agreed with this position (Bovenberg, et. al., 2009).

Genetic feedback in a birth cohort study

The Organisation for Economic Co-operation and Development (OECD) provide guidelines on Human Biobanks and Genetic Research Databases (HBGRD) (2009), which would apply to a birth cohort study that holds biological (DNA) samples from participants. The guidelines state:

The operators of the HBGRD should have a clearly articulated policy on feedback and the nature of feedback, if any, which will be provided to participants.

In certain circumstances, as permitted by applicable law and appropriate authorities, where the participants may be provided with feedback of individual-level results arising from research, the operators of the HBGRD should provide clear information to the participants of the consequences of receiving such results and should inform the participants of their right to opt out from receiving such results. Non-validated results from scientific research using an HBGRD's biological materials and data should not be reported back to participants and this should be explained to them during the consent process (Anon, 2010). More detailed guidelines for feedback have also been provided by a USA National Heart, Lung and Blood Institute Working Group (Bookman et. al., 2006).

Studies of subsets of birth cohort members (or potentially the whole sample) that involve DNA analysis are likely (at present) to use SNPs either to define (or help to define) a subset of participants of particular research interest, or because SNPs may be associated with a character, ability or attribute under study. Research involving DNA sequencing is likely as soon as these procedures become more affordable.

A recent review (Bredenoord et. al., 2011) of ethics discussions about the disclosure of individual genetic data to research participants concludes that the issue is no

longer whether feedback should be given, but how best to select which results are to be returned and how to strike a balance between the possible benefits of disclosure and the harms of unduly hindering biomedical research (and we might add social research). As this review also points out, the right to have, on request, one's personal, genetic and medical data is now recognised in many international and national legal guidelines so the key issue is now what genetic results should be offered to participants. Four criteria have been generally put forward for consideration. Clinical utility (is the information clinically useful in leading to better health), personal utility (is the result of value to the individual), clinical validity (does the genotype accurately and reliably identify or predict a phenotype) and analytic validity (is a genetic result accurately and reliably identified). As already noted in the example of the BRCA study discussed earlier, research findings may well only be indicative and retesting to clinical standards will be required before any action is taken based on the research results. Clinical utility is a key question here.

It has been suggested that a consultation process might be created to set definitions of clinical thresholds that researchers could use. However I am unaware of any progress with such a development. A pragmatic solution would be to follow clinical practice by only considering feedback of genetic information that is already used in clinical practice. This probably means that at present none of the information sought in current and planned studies, or likely to be revealed as an incidental finding in these studies, would reach a threshold where feedback might be considered. However, as long as that is the case, it is important that participants are aware that, if DNA analysis is being carried out with their samples, it is exploratory research which will not reveal information of the kind that can be obtained through the DNA testing carried out in genetic clinics and they will not receive feedback.

However, researchers need to be mindful of other possibilities. Thus far in the discussion only genetic information has been considered. It is possible, indeed likely, that the power of SNP analysis for the prediction of later disease can be considerably sharpened if it is used in conjunction with other information. This could be family history, lifestyle information, assessments of performance or physiological measures. Some of these potential risks – or protective factors – may be amongst the data held by a cohort study. To give a more specific example, there are indications that certain patterns of cognitive performance across childhood and early adult years are associated with later neurodegenerative disease. It is possible that a combination of certain patterns of performance with certain SNPs could provide much stronger predictors than either would alone, and that the possible prediction made using combined results of DNA analysis and other data could be informative for participants.

If it is decided that a genetic result reaches the threshold for potential feedback then the argument based on a duty of care for feedback comes into play. Feedback should then be offered and protocols drawn up about providing information in the consent processes about analysis of the genetic information, decisions about feedback and the process of feedback. In considering appropriate protocols for feedback of genetic information it would be necessary to consider the sometimes complex and statistical risk information that might be involved, and its possible

implications for other family members. This may well mean that following the receipt of feedback, genetic counselling is likely to be involved, together with retesting to clinical standards.

It is important to bear in mind that not all research participants wish to receive predictive genetic information, as indicated in the studies mentioned earlier. The clinical experience of offering predictive genetic tests for late onset Mendelian diseases shows that only a proportion of those who know they are at risk – because of the family history of the disease – will opt for a genetic test to reveal whether or not they have inherited the gene mutation associated with the disease. So, for example, in Huntington’s disease (a rare neurodegenerative condition, which generally develops in mid life and leads to a progressive degenerative function and early death) probably less than 10 per cent of those at 50 per cent risk (i.e. have a parent with the disease) opt for predictive testing. Knowledge of being a mutation carrier can inform reproductive choices but the disease is incurable. For other Mendelian conditions – such as carriers of BRCA1 and BRCA2 mutation – where risk reducing strategies are available, uptake of predictive testing is much higher. However a significant minority still decline the offer of genetic testing.

Thus, the protocol for any cohort study that might reveal genetic information of potential beneficial clinical value and utility for participants would need to include a consent process which informed participants of this possibility and established whether or not they would want to receive feedback.

Thus, it is important in planning any new studies or new sweeps of cohort participants that consideration is given to the possibility that the information (from DNA and other assessments) may be generated or revealed that would be beneficial for participants to know. If it is, then feedback is a possibility and the necessary protocols and consent procedures will be required. It will need to be established whether participants want feedback or not should this become available.

Feedback and the terms of consent

The information leaflet used in the 2002-03 biomedical sweep of the NCDS describes the collection of a blood sample and the storage of portions of the blood and the DNA it contains. The “Letting you know your results” section describes giving participants a summary of measurements made at the assessment and, after a few weeks, fuller feedback. In this context we should note that another cohort study has reported a study of how participants responded to the feedback of blood and weight related results, Lorimer et. al., 2011. The accompanying genetic leaflet makes no mention of feedback. However, the blood samples consent form (consent form 2) does require the cohort member to sign that they understand that “no information found in the DNA will be given to me”. I would suggest that in future participants should be given rather fuller information so they understand that research analyses of DNA are not the same as those that are carried out in a genetic clinic and which can indicate the presence of genetic disease. Such clinical testing will not be carried out and no

information from the DNA research analyses will be fed back (as long as that remains the position).

If a study involving analysis of DNA might reveal clinically significant findings that would be fed back to participants, it would be necessary to seek consent for this and ask participants whether or not they wished to receive feedback. If (or when) we reach a point where a study is planned that could generate data which might be fed back, all participants whose DNA is stored would need to be informed of the protocols that would be followed and future DNA studies.

Selection of subset samples

In the consent process for a subset study, participants are given the usual information about the aims of the study and procedures and data collection involved. Would-be participants are also told why they have been approached. For example, in some studies this could be their geographical location and proximity to an assessment centre, or it could be because they share certain risk factors for a condition or attributes, or they may be a control sample for others who do. The issue may arise of how participants can be informed about why they are being approached without revealing particular genetic or other research information that could give rise to anxieties or concerns. Are researchers duty-bound to reveal the precise selection criteria for every sub sample study? This could be akin to the issue of feeding back genetic information where there is a weak or tentative association between certain SNPs and a disease and so should be avoided. Of course researchers should describe the aims of the research study accurately but in general terms, so that a selected individual is not made aware whether they are in the at risk, control or comparison groups. The aims and purpose of the research should be made clear, as should what participation in a subset study will entail. This way deception is not involved and so it is possible to gain informed consent for such research projects without revealing the genetic or other risk status of the participants.

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Glossary

Single nucleotide polymorphism (SNP, pronounced snip) is a common DNA sequence variation occurring when a single nucleotide – A, T, C or G – in the genome differs between members of a population or between paired chromosomes in an individual. Particular variations in DNA sequences may be associated with the development of diseases or responses to pathogens or drugs or phenotypic attributes or characteristics. Personal genome scans, which are currently sold by some genetic testing companies, identify SNPs and use these to make (tentative) predictions about risks of developing diseases and traits.

Genome-wide association (GWA) studies are those that seek associations between particular common DNA sequence variations (SNPs) and diseases and traits. Two groups of participants – with (cases) and without (controls) – are compared. All participants are genotyped (SNPs are identified). If a particular variant (SNP) is more frequent in the cases, the SNP is said to be associated with the disease or trait under investigation. Associations from GWA studies may be used to estimate the (genetic) risks for an individual (whose SNPs have been identified) developing diseases. Since in most cases SNPs only account for a small proportion of the known genetic risk of common diseases, SNP-based predictive tests are weak and very tentative and are not regarded as being clinically valid. However, the identification of SNPs associated with disease can provide information about physiological processes related to the development of diseases.

Opinions vary about why SNPs can only account for a modest proportion of genetic variation. There may be further associated SNPs to identify. However, these are likely to make a small contribution (those making a larger contribution are likely to be found first). Or there may be a lot of very rare gene mutations, which together make up a significant proportion of the “missing” genetic variation. Other research strategies using gene sequencing are needed to find this variation. There may also be structural variations in the chromosomes, which may contribute and help to fill the explanatory gap left by SNP studies. Or it could be the case that heritabilities have been overestimated so there could be less of a gap than appears to be the case.

Mendelian disease are diseases associated with faults (mutations) in a particular gene. There may be many different mutations of a gene associated with a disease. There are several thousand, mostly very rare, diseases that follow a Mendelian pattern of inheritance in families (e.g. cystic fibrosis, sickle-cell disease, Duchenne muscular dystrophy, BRCA1 / 2 breast cancer, Tay Sachs disease). These may be dominantly inherited (where children have a 1 in 2 chance of inheriting the gene mutation, if it is carried by one parent), recessive (where if both parents are usually normal carriers, children have a 1 in 4 chance of having the disease and a 1 in 2 chance of being a normal carrier) or X-linked (where females are carriers and usually normal but sons have a 1 in 2 chance of inheriting the disease).

The gene mutations associated with Mendelian disease have varying penetrance – that is the chance that someone who inherits the gene with a mutation will develop the disease. But generally penetrance is less than 100 per cent. So in the case of breast cancer and BRCA1/2 and some mutations the chance of developing breast cancer is 50-80 per cent. The age at which you develop the disease, the severity of symptoms, etc may be widely variable. Thus, genetic tests that identify gene mutations cannot usually tell you whether or not you will get the disease, simply whether you have a raised risk of this happening. They may also indicate the severity of the disease.

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