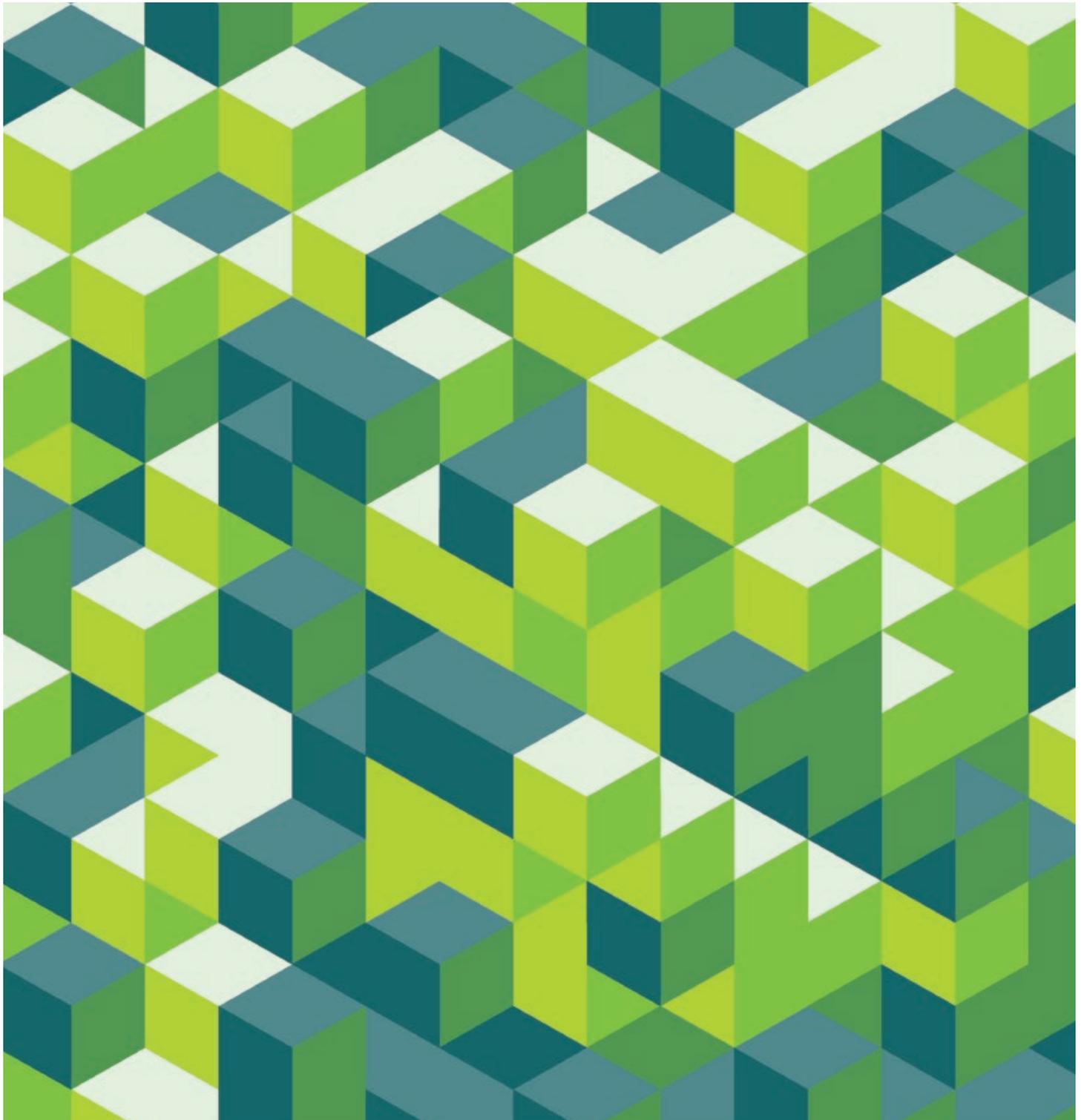


Discussion Paper
June 2015

**UK Biobank
Ethics and
Governance
Council**

Feedback of Health Related Findings: Foreground Principles and Background Perspectives



Contents

1	Introduction	01
	Part One: Foreground Principles	03
2	Guiding Principles and Best Practice	03
	Public good	04
	Beneficence and non-maleficence	05
	Risk/benefit analysis	05
	Reciprocity	06
	Reasonable expectation of feedback	07
	Respect for persons	07
	Consent	08
3	A Principled Position: Defaults, Opt In, and Opt Out	09
	Part Two: Background Perspectives	11
4	The Legal Perspective	11
5	The Human Rights Perspective	18
6	The Preference and Utility Perspective	19
7	The Paternalistic Perspective	22
8	The Practice-Guided Perspective	23
9	Conclusion	23
	Annex A: Feedback policies of a sample of biobanks	24

This report was prepared by the UK Biobank Ethics and Governance Council. The views expressed are those of the Council and do not necessarily reflect the views of its funders, the Wellcome Trust and Medical Research Council, or UK Biobank. Neither the funders nor UK Biobank were involved in the drafting of this report.

1 Introduction

For many years, medical researchers have relied on ‘biobanks’ (that is, collections of biological samples and tissues that are curated and used for particular research purposes). However, we are entering an era of ‘big biobanks’ in which the collection of biological samples is complemented by various kinds of personal data (such as data concerning lifestyles) as well as medical records, all linked to further databases that are health-related (such as cancer registries and hospital episode statistics). The hope that encourages investment in such big biobanks is that, by interrogating the data, researchers will understand much more about the causes of prevalent diseases – in particular, by understanding the causal significance of a person’s genetic profile, their lifestyle, and their exposures, and so on – as well as finding responses that work more effectively for patients.

In at least three respects, today’s big biobanks can be contrasted with yesterday’s biobanks. First, there is the scale and size of the new generation of biobanks. As the name implies, these biobanks are ‘big’, recruiting large populations of participants, not just a small group of people who happen to have a particular disease. For example, UK Biobank, which is an exemplar of a big biobank, has 500,000 participants; Genomics England is aiming to sequence 100,000 genomes; in the United States, the Precision Medicine Initiative is seeking to recruit more than one million volunteers; and, albeit a rather different kind of biobank, 23andMe already has a very large collection of biosamples supplied by its customers. Secondly, big biobanks are created, not for research into one particular disease (such as a cancer or stroke or coronary disease) but as a resource to be available for research into any and all diseases. Thirdly, in big biobanks, when the biological samples are genotyped and sequenced, further data is added to the resource. Moreover, as data linkages intensify, and as biobanks themselves are increasingly linked to one another, it becomes clear that this is where big biobanking and big data meet.

Although there might be some variation in the particulars of big biobanks – for example, whether they are ‘purely’ a research resource or operate in the shadow of clinical practice, whether commercial researchers may use the resource, whether and on what basis they charge researchers, and so on – the prevailing view is that the good governance and legitimacy of big biobanks and their research activities hinges on two fundamental conditions: first, that the interests of the participants (who are the sources of the samples, tissues and data and whose continuing cooperation is essential) should be respected; and,

secondly, that the research activities should be compatible with, or not contrary to, the public interest.

But, what does it mean to require that the interests of the participants are respected; and what does it mean to demand that big biobanks should act in ways that are compatible with the public interest? So far as the first of these questions is concerned, the short answer is that biobanks will respect the interests of their participants so long as they act within the terms and conditions to which their participants have consented. However, a more searching examination of this question would need to go back to the interests that participants have prior to participation and whether the activities of the particular biobank are consonant with those interests (taking account, too, of the way in which participants might have adjusted those interests through their consents). Moreover, to complete the picture, it would be necessary to take into account any competing interests (such as the interests of those who are potential beneficiaries of the research) to be set against the interests of prospective participants as well as any material public interest considerations.¹

Although the private interests of participants cannot be treated as entirely separate from the public interest, in this Discussion Paper, our focus is on the former and, in particular, on the vexed question of whether individual participants in big biobanks have an interest in having health related findings (HRFs) returned to them.² Of course, where the link between individual participants and their samples and data is irreversibly broken, there is no possibility of either the biobank or the researchers who access the resource returning findings. However, for the purposes of this paper, we will assume that participants remain identifiable so that it is possible to return HRFs to particular individuals.

How should we decide whether, prior to participation, individuals have, so to speak, a background interest in the return (or feedback) of HRFs? What is the reference point for this question? A number of candidate reference points suggest themselves, including for example:

1 See, e.g., Henry S. Richardson and Mildred K. Cho, ‘Secondary researchers’ duties to return incidental findings and individual research results: a partial-entrustment account’ (2012) 14 *Genetics in Medicine* 467-472; and, Pilar Ossorio, ‘Taking aims seriously: repository research and limits on the duty to return individual research findings’ (2012) 14 *Genetics in Medicine* 461-466.

2 See, e.g., Catherine Heeney and Michael Parker, ‘Ethics and the Governance of Biobanks’ in Jane Kaye, Susan M.C. Gibbons, Catherine Heeney, Michael Parker and Andrew Smart, *Governing Biobanks* (Oxford: Hart, 2012) 282.

- The positive ‘law’ (national, regional, or international)
- The provisions of ‘soft’ law instruments
- The ethics of human rights and duties
- The general preferences of individuals in conjunction with an ethic of maximising preferences (or utility)
- The best interests of individuals
- The prevailing practice of big biobanks.

In each case, the particular reference point might support or resist recognition of an interest in the return of HRFs; and, not surprisingly, the response that is given to the question of whether prospective participants have a background interest in feedback will depend on which of these reference points is employed.

For present purposes, we will reduce the candidate reference points to five principal ‘perspectives’ that orient the articulation of a feedback protocol. These five perspectives are as follows:

- The legal perspective (being guided by both hard and soft law instruments)
- The human rights perspective
- The preference and utility perspective
- The paternalistic (best interests) perspective
- The practice-guided perspective.

Yet, even with this simplification, it remains unclear which perspective should guide a big biobank’s articulation of its feedback protocol. That said, if the law gave a clear steer in support of feedback, then a biobank would no doubt comply. However, in the absence of a clear legal signal, in the absence of a clearly right approach to the question, and with a considerable degree of uncertainty within each of the perspectives, how should big biobanks proceed?

Currently, the working assumption is that there is no universally right answer, that no one size fits all. In this context, the best advice to big biobanks is to consider all the seemingly relevant factors (particularly the potential harms and benefits associated with giving feedback) and then to take a position that is clearly explained to participants.³ On this view, the imperative is to make it absolutely clear to participants which findings, if any, will be returned and which will not. Similarly, if participants are offered a choice about opting in to feedback or opting out of it (or, at any rate, some set of findings), then this must be carefully explained to participants so that they can exercise their choice on an informed basis. Provided that this

is done, the biobank can fairly say that it has followed best practice and that, whatever background interests participants might have, they are now superseded by the terms and conditions of participation to which participants have consented.

In this Discussion Paper, we seek to shed some light on both the foreground considerations that guide debates about feedback as well as the background against which the question is debated. We will do this in two main parts.

In Part One, we focus on the foreground, setting out and discussing a set of ‘principles for feedback’ that are commonly relied on and that guide contemporary thinking about the return of HRFs. These are principles relating to the public good, beneficence and non-maleficence, risk/benefit, reciprocity, reasonable expectation, respect, and consent. Having addressed these considerations, a biobank’s feedback protocol will reflect a position indicating (i) which findings should be returned, (ii) which findings may or may not be returned, and (iii) which findings should *not* be returned. Quite possibly, of course, the position might not divide HRFs in this way; it might simply place all findings in one of the three categories. Where the biobank’s position is treated as a default, it might then be finessed by giving participants the option of opting in or opting out of certain classes of finding – for example, where findings are in category (ii), the default might be for return unless participants opt out.

In Part Two, we focus on the background by sketching how we might reason if we take one of the five principal perspectives with regard to the specification of the feedback protocol. First, we will start with the perspective that prioritises legal compliance and, in particular, we will consider the significance of the shifting relationship between clinicians and patients as most recently reflected by the UK Supreme Court’s decision in *Montgomery v Lanarkshire Health Board*⁴ – where, in the context of a contested duty to disclose, the Court clearly appreciated that ‘patients are now widely regarded as persons holding rights, rather than as the passive recipients of the care of the medical profession’.⁵ Secondly, we will assess the human rights perspective, the dominant politico/legal/ethical

3 For a clear example of this working assumption and guidance, see Medical Research Council and Wellcome Trust, ‘Framework on the feedback of health-related findings in research’ (London, March 2014) available at: <http://www.mrc.ac.uk/documents/pdf/mrc-wellcome-trust-framework-on-the-feedback-of-health-related-findings-in-researchpdf/>

4 [2015] UKSC 11.

5 [2015] UKSC 11, para 75.

view in Europe. In particular, we will assess the claim that a human right to be informed – and, conversely, a human right ‘not to know’ – should be not only recognised but recognised as encompassing a right to be informed (or not) about the return of HRFs. Thirdly, we will consider the arguments that bear on the preference and utility perspective. Here, the relevant considerations include whether participants have clearly formed preferences about the return of findings, whether the return of findings will be of net benefit to participants (or whether it will do more harm than good), whether researchers have a preference about the return of findings, and whether those who fund big biobanks have a preference relative to their overall research objectives. Fourthly, we will sketch the paternalistic perspective, once dominant in clinical practice but now questionable after *Montgomery*. The core idea in this perspective is that those with the necessary expertise (in this case, the biobank team) should assume the responsibility of judging which HRFs, if any, can be safely and usefully returned to participants. Finally, we will offer some reflections on the practice-guided perspective by drawing on the feedback protocols that have been adopted by biobanks.

Our principal conclusions are as follows.

First, there has been a welcome step change in the practice of biobanks in the way that they deliberate about the ethics of returning HRFs, and in the way that they communicate and explain their feedback policies.

Secondly, the guiding principles suggested by best practice give biobanks considerable leeway in adopting and justifying their feedback position. Biobank A and Biobank B can have diametrically opposed feedback policies; they can appeal to the same set of foreground principles to justify their positions (albeit different principles within the set); and they can both plausibly claim to be examples of best practice.

Thirdly, the idea that ‘no one size fits all’ in relation to feedback policies should not be misunderstood: it is not a licence to play fast and loose with the guiding principles.

Fourthly, greater transparency in the articulation and explanation of biobank positions would be achieved if the key background perspectives to which biobanks orientate their feedback policies were drawn out.

Fifthly, all biobanks will accept that their feedback position needs to be, at minimum, legally compliant. However, so long as the legal position is unsettled, biobanks will necessarily orientate themselves to other considerations in developing their feedback position.

Sixthly, although the context for *Montgomery v Lanarkshire Health Board* is clinical rather than research, it suggests that a constellation of ideas associated with the traditional paternalistic perspective will have significantly less traction in future. Where the question of returning HRFs arises in a clinical context, *Montgomery* applies four square; where the context is not straightforwardly clinical, its application is not mechanical but the spirit of the decision is clear.

Seventhly, as we read *Montgomery*, in future, both the background orienting perspective for big biobanks and the principles that guide best practice need to reflect far more explicitly the idea that participants have rights; and the ethic that shapes biobank practice needs to be appropriately rights-focused.

Part One: The Foreground Principles

In this part of the Discussion Paper, we start by setting out seven guiding principles that best practice suggests should bear on a big biobank’s reasoning in determining its position on the return of HRFs. We then outline the formal shape of a ‘principled position’ and take stock of the limits of current practice.

2 Guiding Principles and Best Practice

On the basis of which principles should a biobank decide whether HRFs should be returned to individual patients or participants? While the literature demonstrates the complexity of this question, there is a growing consensus on the following four points.

First, biobanks have an obligation to ‘determine and make clear to research participants whether [HRFs] will or will not be offered back to the participants’.⁶ Participants should not be unfairly surprised if HRFs are, or are not, returned.

Secondly, even if there is no ‘master’ principle to guide the biobank’s protocol on feedback, a number of ‘principles’ (or general criteria) are relevant and should be given due consideration. Broadly speaking, these principles relate to: the public good; beneficence

⁶ Susan Wolf *et al* ‘Managing incidental findings and research results in genomic research involving biobanks and archived data sets’ (2012) 14 *Genetics in Medicine* 361-384.

and non-maleficence; risk and benefit (relative to the 'best interests' of participants); reciprocity; reasonable expectations; respect for persons; and consent.

Thirdly, where a feedback policy is adopted according to which some HRFs arising from research on 'biobanked' materials should be returned to individual participants, then it is essential to be clear about the particular responsibilities of both the biobank and researchers using the resource.⁷

Fourthly, where participants are invited to take part in tests or activities that will provide further data to enhance the resource, a biobank should not mechanically apply its original feedback policy to these enhancing tests and activities. To this extent at least the feedback position adopted ab initio by a biobank should be treated as reviewable.

In what follows, we will speak to each of the guiding criteria that we have identified above. However, we do so with three important caveats. First, the list is not exhaustive. There is, for example, no *explicit* reference in the list to human rights or human dignity, ideas that pervade modern bioethical debates. Secondly, it is not clear whether the principles pull in the same direction or whether there are tensions between them and, if so, how these tensions manifest themselves. For example, it might be tempting, although no doubt simplistic, to read the first three principles as forming a cluster tending to pull against giving feedback and the latter four principles as forming a cluster tending to push in favour of feedback. Thirdly, it is not clear whether any of the seven principles is 'privileged' or whether they all stand on the same level. So, for example, if a plea is made for an approach to feedback that is 'proportionate' relative to one of the principles, this might imply that the principle in question – say, the public good – is privileged.

Public good

If we understand the concept of the public good in terms of projects that serve the collective interest, that require some level of coordination and cooperation, and that are appropriately facilitated by public resources, then health care research as undertaken by big biobanks certainly qualifies as a public good. Of course, health care is not the only public good and the governance of biobanks might run into difficulties where other public goods (such as criminal justice) are at issue. However, this is not a matter of present concern. The question here is how the pursuit of improved health care and treatment (qua public good) bears on the articulation of a feedback policy. Arguably, the public good, so conceived, has the following three implications for the return of HRFs.

First, attention to the public good demands that any feedback policy should balance the burden on the resource against the benefits of returning HRFs. Feedback may be time-consuming and costly and there is always the possibility that the required staff or other resources cannot reasonably be made available.⁸

Secondly, any policy on feedback should take account of the impact that provision (or not) of feedback may have on the public's perception of the biobank. It would be highly damaging to public trust if it were perceived that feedback policies disregarded either the (personal) interest that participants might have in the return of HRFs or the (altruistic) interest that they might have in the strategic pursuit of health-related research.⁹ Where a biobank has to make a hard choice between these alternatives, the public good would seem most naturally to support the latter.

Thirdly, it is also implicit that the public good requires that the resource be maintained and utilised to maximum effect. If the return of findings impedes these objectives, this is a problem.

Significantly, in a recent study commissioned by the Wellcome Trust and the MRC, it was found that individuals showed little understanding of the impact that obligations to provide feedback may have on researchers' ability to carry out large trials. The report further found that individuals responded differently to questions regarding return of results depending on how the question was framed. If it was made clear that the research would not be able to be carried out were it obligatory to return HRFs they were more likely to support no return of results.¹⁰

7 Lynn Dressler and Eric Juengst 'Thresholds and boundaries in the disclosure of individual genetic research results' (2006) 6 *The American Journal of Bioethics* 18-20.

8 Paul Affleck 'Is it ethical to deny genetic research participants individualised results?' (2009) 35 *Journal of Medical Ethics* 209-213.

9 The Royal College of Radiologists. Management of incidental findings detected during research imaging. London: The Royal College of Radiologists, 2011; Carolyn Johnston and Jane Kaye 'Does the UK Biobank have a legal obligation to feedback individual findings to participants?' (2004) 12 *Medical Law Review* 239-267.

10 'Assessing public attitudes to health related findings in research' (Commissioned by the Wellcome Trust and the Medical Research Council, Conducted by Opinion Leader; 2012) www.wellcome.ac.uk/About-us/Publications/Reports/Public-engagement/WTVM055197.htm (Accessed 23 August 2012).

Benevolence and non-malevolence

These principles focus on protecting the welfare of research participants and tend to be role specific (in the sense that they specifically concern the responsibilities that researchers have to participants).

Benevolence means doing good for the participant and non-malevolence not harming the participant. Generally these principles materialise as two criteria for framing research protocols. Firstly, there should be a balancing of harms and benefits in research – that is to say, possible harms should be proportionate to the benefits of research.¹¹ Secondly, risks to participants should be minimised. Where the principle of non-malevolence dominates that of benevolence, it will accentuate negative obligations rather than any positive obligation to promote the welfare of participants.¹²

A useful analysis of how these principles will impact on obligations to provide feedback is provided by Miller *et al.*¹³ They suggest that an appropriate account of obligations to provide feedback is based on an analysis of the researcher/participant relationship. Rejecting what they describe as legalistic contractual accounts of this relationship (where the focus is on the consent document as providing the extent of the obligations owed by researchers to participants), they suggest that obligations to provide feedback are better based in the principle of benevolence coupled with the professional role that the researcher occupies.

In addition to the internal tension between the directive to do good (benevolence) and the directive to avoid harm (non-malevolence), there are at least three other ways in which these principles are problematic guides.

First, the underlying concepts of ‘benefit’ and ‘harm’ are contested. For example, would it be of benefit to a (presently asymptomatic) participant to be told that researchers have identified a life-threatening and untreatable condition? Or, would this be a harm? From whose standpoint are these matters to be judged? Relative to the biobank and its researchers, participants may have a different understanding of what is a benefit and therefore have a different standard regarding the information they would want to be given.¹⁴

Secondly, where the significance of particular genetic markers is uncertain, is it beneficial or harmful to return findings relating to these markers?

Thirdly, once the analysis of benefit and harm is extended beyond the traditional dyadic focus on researchers and participants, the calculation becomes many times more complex. In an extended frame, the balancing of benefits and harms must also take account of the broader aims of facilitating research which improves the health of the population generally.

Risk/benefit analysis

Where ‘risk’ is understood as some likelihood of harm, then risk/benefit analysis is very closely related to the ideas of benevolence and non-malevolence. So interpreted, risk/benefit analysis dictates that any policy on feedback should take account of the possibilities of harms and benefits that might be expected to result from the return of HRFs.¹⁵

In principle, a risk/benefit calculation might be made from a first person perspective (as when a patient assesses whether the expected benefits of some treatment outweigh the possible harms) or from a third person perspective (as when a clinician assesses whether, in relation to a patient, the expected benefits of some treatment outweigh the possible harms). From a first person perspective, I judge what is in my best interests; from a third person perspective, you judge what is in my best interest. Generally speaking, when biobanks are encouraged to develop their feedback position by undertaking a risk/benefit analysis, or by considering the ‘best interests’ of participants, a third person perspective is presupposed: the question is what the biobank (and its researchers) judge to be in the best interests of participants.¹⁶

11 Christina Davies and Rory Collins ‘Balancing potential risks and benefits of using confidential data’ (2006) 333 *BMJ* 349-51.

12 Franklin Miller *et al* (a) ‘Incidental findings in human subject research’ (2008) 36 *Journal of Law, Medicine, and Ethics* 271-279; Susan M Wolf *et al* ‘The Law of incidental findings in human subjects research: establishing researchers’ duties’ (2008) 36 *Journal of Law, Medicine, and Ethics* 361-383.

13 Franklin Miller *et al* (a) ‘Incidental findings in human subject research’ (2008) 36 *Journal of Law, Medicine, and Ethics* 271-279.

14 Franklin Miller *et al* (a) ‘Incidental findings in human subject research’ (2008) 36 *Journal of Law, Medicine and Ethics* 271-279; Juli Murphy Bollinger *et al* ‘Public preference regarding the return of individual genetic research results: findings from a qualitative focus group study’ (2012) 14 *Genetics in Medicine* 451-457.

15 Martin Richards ‘An ethical review of the use of functional MRI and DNA analysis in birth cohort studies’ (Centre for Longitudinal Studies, 2011).

16 This presupposition is implicit in the MRC and Wellcome Trust Framework (n 3) where, at C(ii), we read: ‘Researchers should consider the potential benefits and harms of providing feedback to individuals of HRFs to ascertain what approach is likely to be in the best interests of participants.’

Taking such a third person perspective, it is clear that provision of feedback not only entails possible benefits for participants but also possible harms, especially when we consider the possibility of participants:

- being caused undue distress, worry and unnecessary invasive investigation by false positive findings;
- altering their behaviour in harmful ways;¹⁷ or,
- finding out about exposures or outcomes which (a) cannot be changed/ameliorated/treated or (b) can only be done so at high cost to the individual financially/socially/emotionally, or at very high cost to the state/health service.

Given that very little systematic research is available on the outcomes of providing feedback, biobanks need to proceed on the basis that the return of findings will have uncertain outcomes and possibly unintended consequences. Ideally, assessments should be built into feedback practices, so that evidence concerning the policy itself can be gathered.

A key issue that arises in relation to risk/benefit analysis is that of which types of HRFs should be fed back. Findings may be of disputed relevance and may not be of a clinical standard. Some argue that questionable findings of this sort should not be fed back.¹⁸ Similarly, questions about whether there needs to be a possibility of clinical intervention lead some to argue that in the absence of such a possibility it would be unethical to provide feedback.¹⁹ On the face of it, different obligations attach to different categories of information. The most straightforward cases are those where the information provided can lead to treatment options or the avoidance of harm, for example blood pressure results. However, the grey

area of assessments and measurements that may be predictive of future disease or where there is less certainty about the possibility of amelioration of any harms are more difficult and probably need to be dealt with on a case-by-case basis.

A risk/benefit analysis may be extended to include possible risks and benefits beyond the individual participants. In particular, it has been recognised that feedback policies will also have consequences for the NHS. There may, for example, be increased consultation rates for GPs following the provision of some kinds of feedback. Conversely, there may be benefits to the NHS if individuals receive health assessments through their participation in a biobank (rather than requesting these from their GP) and if serious conditions are identified early and can be managed to prevent related health complications. Feedback policies need to be evaluated in terms of these likely consequences for NHS resources.

Thus, where a risk/benefit approach is assumed, in considering any feedback or return of results, it is necessary to estimate the costs and resources required to provide this. If such use of resources and costs seem disproportionate to potential benefits for participants and is likely to divert biobanks from their primary purpose of building a resource for research, it might be judged that the provision of individual HRFs is inappropriate.

Reciprocity

Some suggest that obligations to provide feedback are grounded in reciprocity.²⁰ Participants in biobanks give their time and information to the resource and usually do this for no personal gain. In order for a biobank to continue with optimal functioning it requires the on-going cooperation of participants and on-going access to their health information. Given this, it could be that in certain circumstances participants are justified in expecting a biobank to provide some feedback. This principle could be understood as grounded in the broader principles of solidarity²¹ or of justice.²² According to this reasoning, participants deserve feedback because of the contribution they make to the biobank. This principle is especially forceful when the cost to the biobank of providing feedback is minimal.

It has been argued that, if biobanks are to reach their full potential, then better engagement of the public and participants is required and the principle of reciprocity should be at the core of these efforts. Further, it has been suggested that concrete measures such as giving feedback to participants are required.²³

17 Virginia Barbour 'UK Biobank: a project in search of a protocol?' (2003) 361 *The Lancet* 1734-38; Sheela Geraghty *et al* 'Reporting individual test results of environmental chemicals in breastmilk: potential for premature weaning' (2008) 3 *Breastfeeding in Medicine* 207-213.

18 Gaile Renegar *et al* 'Returning genetic research results: points to consider' (2006) 20 *Bioethics* 24-36.

19 Gaile Renegar *et al* (n 18).

20 Jasper Bovenberg *et al* 'Always expect the unexpected: legal and social aspects of reporting biobank research results to individual research participants' (Centre for Society and Genomics, 2009); Susan M Wolf *et al* 'The law of incidental findings in human subjects research: establishing researchers' duties' (2008) 36 *Journal of Law, Medicine and Ethics* 361-383.

21 Compare Ruth Chadwick, Mairi Levitt, and Darren Sickle, 'The Right to Know and the Right Not to Know: the Emerging Debate' in Ruth Chadwick, Mairi Levitt, and Darren Sickle (eds), *The Right to Know and the Right Not to Know* 2nd ed (Cambridge: Cambridge University Press, 2014) 13, esp at 18.

22 Susan M Wolf *et al* 'The law of incidental findings in human subjects research: establishing researchers' duties' (2008) 36 *Journal of Law, Medicine, and Ethics* 361-383.

However, a survey of (Dutch) investigators involved in biobank research showed that, unlike participants, researchers did not endorse a principle of reciprocity which might be used to justify routinely offering certain results to participants.²⁴ Such views also stand out in contrast to one of the guiding principles for biobank research, namely that the focus of reciprocity is on the duty to promote trust between biobanks and participants.²⁵

Reasonable expectation of feedback

In some contexts in which physical investigations or tests take place or scans are taken, it will be perfectly clear that there is a reasonable expectation that the findings will be returned. However, in the context of research biobanking, there is no settled expectation of this kind. To be sure, there is evidence that participants in research projects are not entirely altruistic in their motivations and that they 'expect' some return benefit.²⁶ However, without clear contextual support, the critical question is: by reference to what is a participant's expectation that HRFs will be returned a 'reasonable' one?

The obvious reference points for the reasonableness of such an expectation are:

- The law (i.e., the law requires researchers to return HRFs)
- The literature and information sheets inviting participation indicate that HRFs will be returned (it would be scandalous if a biobank then relied on the 'small print' of the protocol to deny any entitlement to the return of HRFs)

- The general practice of biobanks
- One of the other standard considerations (for example, it might be argued that 'reciprocity' or 'respect for persons' or 'beneficence' or an overwhelming balance of benefit over risk supports the return of HRFs and, thus, shows that the expectation is reasonable).

In this context, a biobank might judge that the most important thing is to manage the expectations of participants. Certainly, where all the information from the biobank emphasises that the project is purely for research purposes and, in no sense, a health check or diagnostic, then any participant who claims to have a reasonable expectation that HRFs will be returned will have received no encouragement from the biobank and will need to look to some other reference point in order to support the claim.

Respect for persons

The principle of respect for persons can be articulated in more than one way. In a broad articulation, it requires favourable consideration to be given to the self-interested preferences of each person (in the way that preference utilitarian ethics prescribes). However, in much ethical thinking, respect for persons presupposes that persons have rights and that what is to be respected is specifically the set of rights that each person has. In this latter articulation, the rights to be respected will often be designed to facilitate the autonomy of the individual; and this, in turn, will generate various informational rights, including a right to be informed.

It is broadly accepted in the literature on feedback that HRFs should only be returned when participants have consented to being given feedback.²⁷ Some participants may not wish to receive feedback and if this is the case then respecting such individuals' autonomous wishes means respecting their decision not to receive feedback (participants having either waived the benefit of their right to know or exercised their so-called right not to know').²⁸ This can be difficult for biobankers and researchers, particularly if the results/findings show the possibility of serious harm that could be easily avoided. However, it is a difficulty shared by well-intending paternalistic clinicians who find that 'respect for the patient' stands in the way of improving the patient's health or quality of life.

Respect for autonomy has broad implications for how we frame obligations to return HRFs. Often, discussion of such obligations focuses on the possibility of averting harm to individual participants – so it might be said that there is only an obligation to provide feedback where

23 Herbert Gottweis *et al* 'Connecting the public with biobank research: reciprocity matters' (2011) 12 *Nature Reviews Genetics* 738-739.

24 Tineke M Meulenkamp *et al* 'Researchers' opinions toward the communication of results of biobank research: a survey study' (2011) 20 *European J. Human Genetics* 259-262.

25 Public Population Projects in Genomics and Society (P3G). Policy statement 'Population studies: return of research results and incidental findings' (December 2011).

26 See, e.g., Jasper Bovenberg *et al* 'Always expect the unexpected: legal and social aspects of reporting biobank research results to individual research participants' (Centre for Society and Genomics, 2009); and Hélène Nobile 'Why do participants enroll in population biobank studies? a systematic literature review' (2013) 13 *Expert Rev. Mol. Diagn.* 35-47.

27 Carolyn Johnston and Jane Kaye 'Does the UK Biobank have a legal obligation to feedback individual findings to participants?' (2004) 12 *Medical Law Review* 239-267.

28 See Ruth Chadwick, Mairi Levitt and Darren Shickle (eds), *The Right to Know and the Right Not to Know 2nd ed* (Cambridge: Cambridge University Press, 2014).

there is a possibility of significant clinical benefit.²⁹ Such a policy may not, however, meet the standards of showing respect for persons. Respect for persons may be interpreted to mean that participants should be provided with all information which ‘relates to them’ regardless of whether it has any clinical significance.³⁰

Consent

It is commonly agreed that participants may be held to the terms and conditions for participation in a biobank only where they have freely consented to enrol on those terms. However, this does not speak to whether the terms and conditions should provide for the return of HRFs. Indeed, unless it is proposed that no feedback protocol should be put to participants unless it is one to which a rational or a reasonable person would consent, it is unclear how consent is a relevant consideration for the purposes of determining what the protocol should say about the return of HRFs. And, if the test were one of what a rational or a reasonable person would consent to, the critical concepts would be those of rationality and reasonableness.

That said, once the protocol has been developed, and once participants have consented to it, then, as we pointed out in our introductory remarks, the short answer to whether feedback should be given will be provided by the terms and conditions to which participants have consented. Furthermore, if it is asked why the terms and conditions should govern the relationship between the biobank (and researchers who access the resource) and participants, the answer is that participants have consented to these terms and conditions.

Consent to a ‘no feedback’ protocol notwithstanding, some might argue that HRFs should be returned to participants. In other words, as Miller *et al* put it, researchers should not be able to ‘contract out’ of their ethical obligation to give feedback.³¹ The logic of such an argument is that participants have a background right to the return of findings which is either indefeasible (i.e. cannot be waived) or, on the facts, has not been waived. For example, it might be argued that the biobank did not take sufficient steps to highlight the significance of the participant’s consent in relation to the return of HRFs – in other words, the consent was not adequately informed; or an exculpatory consent clause is construed restrictively against the biobank.³² This argument alerts biobanks to several things: first, to the importance of ensuring that the consent given by participants is sufficiently informed; secondly, to the importance of plain, intelligible and unequivocal drafting; and, thirdly, to the possibility that participants might have background interests in the return of HRFs that are non-negotiable – although the burden of justifying such a strong claim is surely on participants.

There is also the converse possibility that, consent to a ‘feedback’ protocol notwithstanding, some might argue that HRFs should *not* be returned to participants. Here, the argument is that it is a mistake to assume that, where A (the biobank) has the consent of B (the participant) to do act x (return HRFs to B), this is a sufficient justification against all-comers (this being the so-called ‘fallacy of sufficiency’). According to this analysis, what B’s consent entails is that A does no wrong to B by doing x (B has authorised A to do x). However, even in a community that is organised around rights, A’s doing of x might constitute a wrong in relation to C or D; and there might be cases where doing x raises question of public wrong that go beyond the relationship between A and B.³³

29 Vardit Ravitsky and Benjamin S. Wilfond ‘Disclosing individual genetic results to research participants’ (2006) 6 *The American Journal of Bioethics* 8-17.

30 Vardit Ravitsky and Benjamin S. Wilfond (n 29).

31 Miller *et al* (n 13). Susan M Wolf *et al* ‘The law of incidental findings in human subjects research: establishing researchers’ duties’ (2008) 36 *Journal of Law, Medicine, and Ethics* 361-383.

32 Loane Skene ‘Feeding back significant findings to participants and relatives’ in Kaye and Stranger (eds) *Principles and Practice in Biobank Governance* (Ashgate Publishing, 2009).

33 Roger Brownsword ‘Rights, responsibility and stewardship: beyond consent’ in Widdows (ed.) *The Governance of Genetic Information: Who Decides?* (Cambridge University Press, 2009) 99-125. Brownsword also argues against what he calls ‘the fallacy of necessity’, this being the mistake of assuming that A will always do wrong to B if B objects to A doing x. From a rights perspective, this overstates the relevance of consent: it is only if B has a right that A should not do x, that B’s consent becomes an issue.

3 A Principled Position: Defaults, Opt In, and Opt Out

Having given due consideration to the relevant principles, big biobanks are advised to take a position on the return of findings to participants. The position so taken might be straightforward and non-negotiable: there is to be no feedback, or there is to be some level of feedback. Or, it might be more complex but still non-negotiable – for example, the biobank might reserve a discretion to give feedback in certain circumstances. Alternatively, the biobank might adopt a default position (again, for no feedback or for some level of feedback) but participants are given some choice about whether or not to have HRFs returned – for example participants might be invited to opt in to the return of HRFs or to opt out of their return.

It is implicit in the above remarks that a biobank might want to discriminate between different kinds of HRFs. The range of HRFs might include: routine clinical assessment findings; potential clinically significant findings (including indications of existing disease or abnormality and risk factors predictive of serious disease); environmental exposure information; and genome analysis data and results of research conducted on the resource. For each category of HRF, the biobank might want to set a tailored feedback policy; and, the more that bespoke policies are set for particular categories of HRFs, the more complex the feedback policy will become.

Furthermore, a biobank might want to differentiate between primary and secondary findings. For example, the position apparently taken by Genomics England for the 100,000 Genomes Project is that, whereas primary findings will be returned to patients/participants, with no possibility of opt out, secondary findings will be returned on an opt-in basis (see Annex A). Again, with each refinement of this kind, the feedback position becomes more complex.

The degree of complexity of the feedback position notwithstanding, the type of HRF will necessarily fall into one of three categories in the following way. The particular HRF is treated as one that:

- (a) *should* be fed back (i.e. feedback is required)
- (b) *may* be fed back (i.e. feedback is permitted)
- (c) *should* not be fed back (i.e. feedback is prohibited).

If the biobank operates with a default policy, the default classification might be subject to the participant's election. For example, a participant might have opted out of feedback where the HRFs are otherwise in categories (a) or (b); or, a participant might have opted in to feedback where the HRFs are otherwise in categories (c) or (b).

So much for the formal shape of the biobank's feedback policy. What will drive the *substance* of the policy, what will determine whether the policy is to return some or all HRFs, is which of the guiding principles are prioritised.

In a seminal paper, Wolf et al³⁴ recommend what should generally fall in each of the three basic categories (should, may be, and should not be fed back) whilst recognising that this is really the starting point and that biobanks may further modify these criteria in a way that is sensitive to the biobank population and biobank research design:

- (a) “researchers in the biobank research system *should* offer to return IFs [incidental findings] and IRRs [individual research results] that meet all of the following criteria:
 - The findings are analytically valid;
 - Returning them to the contributor [participant] comports with applicable law, including CLIA³⁵ (which may require ascertaining or verifying results in a CLIA-certified lab);
 - The contributor has been offered the option of consenting to return of individual findings (either in the initial informed consent process, or in a subsequent consent process that may be a request for an individual's consent or part of a larger effort to elicit many contributors' consent) and has opted to receive them³⁶;
 - The findings reveal an established and substantial risk of a serious health condition; and
 - The findings are clinically actionable, meaning that return of findings of health importance allows the contributor or contributor's clinician to take action with significant potential to prevent or alter the course of the condition or to alter its treatment.”

34 Susan Wolf et al 'Managing incidental findings and research results in genomic research involving biobanks and archived data sets' (2012) 14 *Genetics in Medicine* 361-384.

35 “Congress passed the Clinical Laboratory Improvement Amendments (CLIA) in 1988 establishing quality standards for all laboratory testing to ensure the accuracy, reliability and timeliness of patient test results regardless of where the test was performed.” Information taken from <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm> (accessed 23 August 2012).

36 The alternative being that an individual has been offered feedback but has exerted their 'right not to know'.

(b) “researchers in the biobank research system may offer to return IFs and IRRs that fail to meet the above criteria, if they instead meet *all of* the following criteria:

- The findings are analytically valid;
- Returning them to the contributor comports with applicable law, including CLIA (which may require ascertaining or verifying results in a CLIA-certified lab);
- The contributor has been offered the option of consenting to return of individual findings (either in the initial informed consent process or subsequently, as indicated above in (a)) and has opted to receive them; and
- The findings reveal an established and substantial risk of likely health or reproductive importance or personal utility to the contributor and return is likely to provide net benefit from the contributor’s perspective.”

(c) “researchers in the biobank research system [should] *not return* IFs and IRRs offering unlikely net benefit from the contributor’s perspective, including findings whose likely health or reproductive importance or personal utility cannot be ascertained.”

But, which principles drive this default classification? Beyond the analytical validity of the findings, the key principles are (i) beneficence and non-maleficence in conjunction with (ii) respect for the participant’s wishes in relation to the return of HRFs. Although the latter is expressed in the language of consent, it seemingly presupposes a right not to know and the importance of respect for persons.

On its own terms, the scheme presented by Wolf *et al* needs some modification to deal with cases of uncertainty, i.e., where what the finding reveals or indicates is the possibility (but no more) of a serious health condition. In such a case, quite possibly, the principle of beneficence and non-maleficence will be supplemented by its near cousin the principle of risk/benefit. However, the more serious point is that the scheme is vulnerable to the objection that it strikes a middle course that undervalues principles (such as that of reciprocity and reasonable expectation) that push for more extensive feedback as well as those (such as public good) that probably militate against feedback. That said, any scheme that prioritises only

some of the principles will invite a similar objection and a scheme that claims to give due weight to all the principles will invite the different objection that it simply lacks coherence.

Taking stock

In 2012, Johnson *et al* published the results of the empirical work that they had undertaken to examine and document the management and return of individual research results (IRRs) and incidental findings (IFs) to research participants among biobanks.³⁷ 2,366 documents were analysed, covering 85 biobanks, with the conclusion being that only about a half of biobanks address return of IFs and IRRs in their publicly available documents and few biobanks suggest that IFs or IRRs should be returned. The authors conclude that given the growing agreement that researchers have a responsibility to determine and make clear to research participants whether or not IFs and IRRs will be returned, it seems reasonable to suggest that biobanks should be more explicit about their policies in this regard.

Bearing in mind the findings made by Johnson *et al*, there can be no doubt that best ethical and governance practice at big biobanks has already come a long way. Compared to a state of affairs in which biobanks fail to consider their approach to HRFs, fail to communicate it to their participants, and fail to explain and justify their policy and position, the present state of affairs is a huge leap forward. It is understood that the ethics and governance of big biobanks matters and there is no doubt that the feedback responsibilities of researchers is a question that is now taken extremely seriously.

Nevertheless, best practice is relatively undemanding. While the shape of a principled position in relation to the return of HRFs can be discerned, the substance of the biobank’s position will be dictated by the particular principles that are prioritised. No one doubts that biobanks address the principles in a good faith attempt to articulate a defensible feedback position. However, there is so much discretion within the range of principles that biobanks can come up with diametrically opposed feedback policies and still plausibly claim to be justified in doing so. For example, while a biobank that has a rigid no feedback policy may justify its position by invoking those principles that militate against feedback, a biobank that has a rigid return of HRFs policy may appeal to those principles that most naturally push in favour of feedback – and, to repeat, provided that those principles are in the recognised range, no further justification will be required.³⁸

37 Gina Johnson *et al* ‘An empirical examination of the management of return of individual results and incidental findings in genomic biobanks’ (2012) 14 *Genetics in Medicine* 444-450.

Part Two: Background Perspectives

It should be emphasised that these remarks do not cut against the view that no one size feedback protocol fits all. The ‘all’ that cannot be fitted to the one size is the different kinds of research findings. Some findings are fit for return, some are not, and some might be. This is the basis of Wolf *et al*’s scheme. It does not follow, though, that the guiding principles may be legitimately used in a ‘pick and mix’ manner. A principled position demands more than that. Yet, other than a good faith exercise of the discretion afforded by the principles what more might ethicists require?

We suggest that a fuller account of a particular principled position calls for some connection with the background considerations that are in play. It might be too much to expect that, by clarifying these background considerations we can improve the deep justification of a biobank’s approach to the return of HRFs, but at least there would be greater transparency. In this spirit, we turn in the second part of the paper to the background.

In this part of the Discussion Paper, we seek to shed some light on the background normative order against which the principles operate. We do this by drawing out five basic ‘perspectives’ that offer pathways that lead from the background, through the principles, to the articulation of a biobank’s position on the return of HRFs. These perspectives are respectively: the legal; the human rights; the preference and utility; the paternalistic; and the practice-guided.

4 The Legal Perspective

It hardly needs to be said that, for any biobank, legal compliance will be a minimum requirement. To be sure, some big biobanks might wish to be super-compliant, going beyond their legal obligations to participants; but, in all cases, at the very least, biobanks must comply with their regulatory obligations.

What, then, is the legal position in relation to the return of HRFs? In principle, English law might require, permit, or prohibit the return of HRFs made by biobanks (and by researchers who access biobank resources). In the absence of any legislative provision dealing with this matter, the answer hinges on common law principles and, in particular, on the basic principles of tort law. It should be emphasised, though, that discussion of any legal obligation to provide feedback is bound to be speculative as the law in this area is ambiguous and it has not been litigated on.³⁹ We will focus shortly on tort law but, before we do so, it is as well to be aware that feedback policies might engage other areas of law, including the following:

- a) Contract law: although the relationship between a biobank and its participants takes the form of a contract – participants agreeing to participate in return for certain undertakings and assurances given by the biobank – this is a long way from a market exchange. Given that English law requires that the parties to a contract intend to create legal relations,⁴⁰ it seems doubtful that the terms and conditions of participation (including the feedback protocol) would be treated as a legally enforceable contract. If, contrary to this view, the transaction were to be treated as legally enforceable, the terms and conditions would require interpretation; and it might well be that exculpatory ‘no feedback’ exemption clauses in the consent forms would *not* hold up and would be interpreted against the party who seeks to rely on them.⁴¹ Moreover, if the policy on feedback is unclear the prospect of successfully relying on such clauses is weakened.

38 Compare Kadri Simm, ‘Biobanks and feedback’ in Ruth Chadwick, Mairi Levitt, and Darren Shickle (eds), *The Right to Know and the Right Not to Know* 2nd ed (Cambridge: Cambridge University Press, 2014) 55, esp at 63 (‘Both camps of the for and against disclosure are essentially juggling with the same set of principles and values, just ranking them differently’).

39 Jane Kaye *et al* ‘Ethical, legal and social issues arising from the use of GWAS in medical research: literature review for the Wellcome Trust’ (HeLex, 2009); Loane Skene ‘Feeding back significant findings to participants and relatives’ in Kaye and Stranger (eds) *Principles and Practice in Biobank Governance* (Ashgate Publishing, 2009).

40 *Balfour v Balfour* [1919] 2 K.B. 571.

41 Susan M Wolf *et al* ‘The law of incidental findings in human subjects research: establishing researchers’ duties’ (2008) 36 *Journal of Law, Medicine, and Ethics* 361-383; Loane Skene ‘Feeding back significant findings to participants and relatives’ in Kaye and Stranger (eds) *Principles and Practice in Biobank Governance* (Ashgate Publishing, 2009).

- b) Research governance documents: ‘guidance in this area is not explicit, is ambiguous and is hard to find in ethics and regulatory instructions’.⁴² Notwithstanding this, such guidance must be followed and when analysing whether any duty of care has been breached guidance may be important in terms of setting the standard for reasonable care.⁴³
- c) Confidentiality: any policy on feedback would need to take care not to breach the confidentiality of research participants. Although there may be occasions where breaching confidentiality is necessary such occasions should be handled with care and where possible participants need to be informed that disclosure is going to occur.
- d) Human rights law: in their seminal paper, one of Johnston and Kaye’s arguments is that, where a biobank is a ‘public authority’, then it may have a duty to warn of dangers to life in accordance with article 2 of the Human Rights Act 1998. The Human Rights Act 1998 enshrines in domestic law the key provisions of the European Convention on Human Rights (ECHR). The duty to warn under article 2 of the ECHR was the subject of litigation in *Osman v UK*.⁴⁴
- e) Administrative law: again, if a biobank is a public authority then any policy on feedback may be subject to judicial review. For the purposes of our discussion the most pertinent standard here would be whether any such policy, or exercise of discretion, was *reasonable* (or *unreasonable*, in the sense either of defeating a legitimate expectation or being utterly unreasonable).⁴⁵ The policies of other similarly constituted biobanks may impact on how reasonableness is interpreted.

Turning now to the possibility of a tort claim, let us suppose that a participant is aggrieved that HRFs have not been returned to him or her. Then, according to English tort law, this participant claimant will need to establish: (i) that the biobank, or the researchers, have a duty to inform him or her; (ii) that they were in breach of that duty; (iii) that there was a sufficient causal link between the failure to inform and the harm that resulted; and (iv) that the resulting harm is of a kind recognised by the law. We comment below on some of the main elements of such a claim.

Duty of care

Stated rather generally, English tort law is geared to compensate claimants where wrongful acts cause them physical or psychological injury, damage to their property, or harm to their reputation. Where the claimant suffers a purely economic loss arising in a transactional context, the compensatory claim will usually be pleaded in contract rather than tort. Potentially, the gist of a tort claim against a biobank might fit pretty well with a standard negligence claim. For example, the claimant might allege that the biobank has carelessly returned HRFs to him or her when it knew that he or she had opted out of feedback; or the allegation might simply be that the biobank was careless in giving the participant misleading or inaccurate or poorly understood information.⁴⁶ Cases of this kind would seem to be reasonably straightforward. However, what if the claimant’s grievance was that the biobank (in line with its feedback policy) had not returned HRFs and that, in consequence, treatment of a particular condition was delayed to the detriment of the claimant? Such a claim would be much less straightforward, there would not be clearly applicable precedents to guide the court, and there would need to be a resort to very general principles.

In cases that are less than straightforward, establishing a duty of care in a legal sense involves the following three-part test as set out in *Caparo Industries v Dickman* [1990] 1 All ER 568:

- a) Is there a harm the risk of which is foreseeable?
- b) Is there sufficient proximity between the parties?
- c) Is it fair, just and reasonable to impose a duty of care?

Applying this test to the case of feedback and biobanks it is arguable that in some instances a duty of care could be established. This is true for both biobankers and researchers as independent professionals and also the biobank as an entity in itself.⁴⁷

42 The Royal College of Radiologists. Management of incidental findings detected during research imaging. London: The Royal College of Radiologists, 2011.

43 The Royal College of Radiologists. Management of incidental findings detected during research imaging. London: The Royal College of Radiologists, 2011; Frances Lawrenz and Suzanne Sobotka ‘Empirical analysis of current approaches to incidental findings’ (2008) 36 *Journal of Law, Medicine, and Ethics* 249-255.

44 Carolyn Johnston and Jane Kaye ‘Does the UK Biobank have a legal obligation to feedback individual findings to participants?’ (2004) 12 *Medical Law Review* 239-267.

45 Carolyn Johnston and Jane Kaye (n 44).

46 Compare Sheela Geraghty *et al* ‘Reporting individual test results of environmental chemicals in breastmilk: potential for premature weaning’ (2008) 3 *Breastfeeding in Medicine* 207-213; See also Mary Dixon-Woods *et al* ‘Receiving a summary of the results of a trial: qualitative study of participants’ views’ *BMJ*, doi:10.1136/bmj.38675.677963.3A (published 9 January 2006).

The nature of the information that is being provided to the participants will be relevant to the question of whether there is a duty of care. A clear case can be made for returning HRFs when the information is such that there is a harm that is foreseeable and could potentially be avoided (through possible treatment).⁴⁸

The question then becomes one of proximity. Johnston and Kaye argue that, when a biobank collects extensive data, and follows up participants through their health records for many years, then this on-going relationship provides sufficient proximity between the biobank and the participant to establish a duty of care.⁴⁹ If the claimant were a third party – such as a member of the participant’s family – there would probably not be sufficient proximity to establish a duty of care although there might be a duty to warn participants and suggest that they warn third parties.⁵⁰ For example, genetic feedback may have implications for a participant’s family and, if a biobank gathers information about environmental exposures, high levels of pollution could have serious implications for not just the participant but also others who are exposed. In the latter situation there is a possibility of avoidance of serious harm and the provision of such information is not likely to be onerous.⁵¹

However, even if the tests of foreseeability and proximity are satisfied, there remains the question of whether it would be fair, just and reasonable to impose a duty of care in the particular circumstances. No matter how it is wrapped up, this question amounts to an open-ended test of reasonableness.

With regard to what is ‘reasonable’, two considerations that might militate against imposing a duty on a big biobank or those who access its resource are as follows:

47 Carolyn Johnston and Jane Kaye ‘Does the UK Biobank have a legal obligation to feedback individual findings to participants?’ (2004) 12 *Medical Law Review* 239-267; Jane Kaye *et al* ‘Ethical, legal and social issues arising from the use of GWAS in medical research: literature review for the Wellcome Trust’ (HeLex, 2009).

48 Although how ‘clinically significant’ is defined is in itself controversial. See Robin Z Hayeems *et al* ‘Not so simple: a quasi-experimental study of how researchers adjudicate genetic research results’ 2011 (19) *European Journal of Human Genetics* 740–747.

49 Carolyn Johnston and Jane Kaye ‘Does the UK Biobank have a legal obligation to feedback individual findings to participants?’ (2004) 12 *Medical Law Review* 239-267.

50 Jane Kaye *et al* ‘Ethical, legal and social issues arising from the use of GWAS in medical research: literature review for the Wellcome Trust’ (HeLex, 2009).

51 Compare *Tarasoff v. Regents of University of California*, 17 Cal.3d 425.

52 [2015] EWHC 1394 (QB).

(i) that, while it might be reasonable to impose such a duty in a clinical context, it is not reasonable to do so in a research context; and (ii) that the policy of the law is to be very cautious in imposing positive duties on persons – and a responsibility to return HRFs would be such a positive duty.

Given the spread of big biobanks into clinical contexts as well as hybrid clinical/research contexts, the question of whether the duties of biobanks vary from one context to another will need to be addressed. We cannot undertake an analysis of this matter here but it adds to the uncertainty of the legal situation.

So far as positive obligations are concerned, it is undoubtedly correct to say that English tort law (unlike some other common law and civilian regimes) has been extremely slow to recognise such responsibilities. If there were any doubt about this, the reluctance of English law to recognise positive duties or to impose liability for omissions has been underlined by the recent decision of the High Court in *ABC v St George’s Healthcare NHS Trust*.⁵² There, the claimant, who was pregnant at the relevant time, brought an action in negligence against the defendants, complaining that they had failed to inform her that her father had been diagnosed with Huntington’s Disease. Had the claimant been so informed, she would have known that she was at risk of having the disease, she would have known that her children would also be at risk, and she would have terminated the pregnancy. For the purposes of hearing the defendants’ application to strike out the claim, it was conceded that the first two limbs of the *Caparo* test were satisfied. However, the defendants advanced no fewer than nine reasons why it would not be fair, just, and reasonable to impose the duty. In one way or another, these reasons all hinge on the fact that the defendants obtained the information about the father’s health status in confidence. To tell the claimant daughter that her father had Huntington’s Disease would be to break the confidence; and English law sets the bar very high before a confidence may be broken – indeed, higher than that set by bodies such as the Human Genetics Commission, the Nuffield Council on Bioethics and the GMC (where the importance of alerting family members to genetic risks is recognised). Faced with this barrage of arguments favouring respecting the confidence, coupled with the absence of a clear precedent in support of the claimant’s case, Mr Justice Nicol agreed that the claim should be struck out.

By striking out the claim, the court in the *St George's Healthcare NHS Trust* case was signalling that this action had no chance of success. Does it follow then that the view that biobanks should return HRFs where the situation is analogous to an 'easy rescue'⁵³ (i.e. where A is in a position to save B and this would be at limited cost to A) has no chance of being supported in English law? For several reasons, we do not think that it does. First, the reasoning in the *St George's Healthcare NHS Trust* case exemplifies the approach of a court that is minded to stay safely within the settled law. Unless the claimant thought that an appeal court might rewrite the law (which, of course, does happen from time to time), there would be no point in appealing from such a conspicuously safe decision. Secondly, the fact that the claimant could not cite a precedent that was on all fours with the case would be irrelevant if a court were minded to break new ground; the whole point about a ground-breaking decision is that it is the first of its kind. Thirdly, the *Montgomery* decision, which we deal with below, is arguably just such a ground-breaking decision and it would have been interesting to see what Nicol J would have made of the claim if the general principle (not the particular facts) of *Montgomery* had been presented in argument. Finally, it was absolutely critical to the thinking in the *St George's Healthcare NHS Trust* case that there was no way of telling the claimant other than by breaking a confidence – and, to make the obvious point, this is simply not a factor that will normally be material in a claim against a biobank for failure to inform.

This last point exposes a weakness in the jurisprudence. When a court asks whether it would be fair, just and reasonable to recognise a duty, it elides two questions: (i) whether there is a prima facie duty; and (ii) if so, whether that duty prevails in the event of there being conflicting duties. What the *St George's Healthcare NHS Trust* case leaves unclear is whether the court (i) declined to recognise a prima facie duty

to be informed or (ii) recognised a (weak) prima facie duty to be informed but treated it as outweighed by a (stronger) conflicting duty of confidence. From the claimant's perspective it matters little whether the court is reasoning in one way or the other; either way the claim fails. However, for the purpose of judging whether the *St George's Healthcare NHS Trust* case would militate against a claim made against a biobank, the difference is important. If the court recognises a weakish duty to inform, potentially outweighed by other considerations (including questions of confidentiality), then in the absence of issues of confidentiality the burden is on the biobank to come up with other reasons that will outweigh the prima facie right of participants.

Finally, it is worth mentioning one other feature of the *St George's Healthcare NHS Trust* case. The claimant's father, having shot the claimant's mother, was convicted of manslaughter. Subsequently, from time to time, the claimant and her sister attended one of the defendants' clinics for 'family therapy'. It was conceded that the defendants might well have owed the claimant 'a duty of care in the way in which they carried out the family therapy.'⁵⁴ The fact that there was this prior relationship between the claimants and the defendants might have enabled the claimant to argue for the duty to inform as an extension of the prior duty. However, the court would not accept that the obstacle presented by the confidential nature of the information could be circumvented by pleading the case in this different way. Such a pleading, though, might be more successful where there is no difficulty about confidentiality; and, in this respect, claims made by participants who have a prior and ongoing relationship with a biobank, and to whom there clearly is a duty of care of some kind, seem relatively strong.⁵⁵

Breach of duty

Once a duty of care is established we need to consider whether a biobank breaches this duty by not providing feedback. In order to establish a breach it must be shown that not returning HRFs (even if in line with the feedback protocol) would be unreasonable. Prior to the recent decision of the Supreme Court in *Montgomery v Lanarkshire Health Board*,⁵⁶ reasonableness would have been assessed in accordance with the so-called *Bolam* standard which states that negligence can only be established if the behaviour is not

in accordance with a practice accepted as proper by a responsible body of medical men skilled in that particular art.⁵⁷

53 See, e.g., Heeney and Parker (n 2) at 296.

54 [2015] EWHC 1394 (QB), para 22.

55 It should be noted that, in specific circumstances, a rule of rescue might be coupled with the doctrine of necessity. The doctrine of necessity allows for actions to be taken that while not ordinarily permissible are allowed because they are *necessary* to achieve a particular end. As applied to the disclosure of information to participants it is most likely the doctrine of necessity would be invoked to justify *disclosure* of information (a no feedback policy, or opt out election, notwithstanding) when there is certainty of an immediate and serious danger which can be averted through disclosure. This, however, sheds no further light on whether a biobank's adoption and observance of a no feedback position is likely to be problematic relative to background tortious responsibilities.

56 [2015] UKSC 11.

So, in order to assess whether any policy is ‘reasonable’ we would need to look to the ‘responsible’ policies of other similarly constituted biobanks. Given the variety of feedback policies adopted by biobanks (a sample can be found in Annex A), unless the defendant biobank were an extraordinary outlier, it should be relatively easy to argue that the position under scrutiny was in line with that adopted by at least some other comparator biobanks. However, the *Bolam* standard, having been criticized over an extended period, has now been severely disrupted by the patient-centred (and potentially participant-centred) approach in *Montgomery*. And, in the wake of *Montgomery*, it is necessary to reconsider both the question of a big biobank’s duty of care and the circumstances in which it would be held to be in breach of the duty.

After *Montgomery*

In *Montgomery*, two questions of law arose for decision. The first question was whether the claimant’s doctor had a duty to inform the claimant (who suffered from diabetes) of the risk of shoulder dystocia (where the baby’s shoulders cannot pass through the pelvis) associated with a vaginal birth; and, concomitantly, whether the claimant should have been offered the possibility of delivery by elective caesarean section (CS). The claimant, it should be said, was *not* told about the risk and was *not* offered the option of a CS delivery. The second question was whether, if the option of CS delivery had been given to the claimant, she would have accepted it (or, stated more accurately, whether it was more likely than not that the claimant would have elected to have a CS delivery).

Most of the main judgment in the Supreme Court (this being given by Lords Kerr and Reed, with Lords Neuberger, Clarke, Wilson and Hodge agreeing) is devoted to the first question. The gist of the judgment is that the old *Bolam*-based law fails to reflect the reality of the modern relationship between doctors and patients. Traditional paternalism belongs to another age; today, patients expect to be informed and to make their own choices. Hence, whether or not the defendant could point to a body of responsible medical opinion or practice that supported her suppression of the risk and the option of CS was no longer the question. The question today is whether the doctor has taken reasonable care to ensure that the patient is aware of any material risks; and the test of

materiality ‘is whether, in the circumstances of the particular case, a reasonable person in the patient’s position would be likely to attach significance to the risk, or the doctor is or should reasonably be aware that the particular patient would be likely to attach significance to it.’⁵⁸ Judged by this test, the defendant was in breach of the duty of care owed to her patient.

So much for the short version of the first question in *Montgomery*. In order, to appreciate the landmark nature of the case, however, the core section of the judgment needs to be digested. The critical paragraphs are as follows:

Conclusions on the duty of disclosure

74. The Hippocratic Corpus advises physicians to reveal nothing to the patient of her present or future condition, “for many patients through this cause have taken a turn for the worse” (*Decorum*, XVI). Around two millennia later, in *Sidaway*’s case Lord Templeman said that “the provision of too much information may prejudice the attainment of the objective of restoring the patient’s health” (p 904); and similar observations were made by Lord Diplock and Lord Bridge. On that view, if the optimisation of the patient’s health is treated as an overriding objective, then it is unsurprising that the disclosure of information to a patient should be regarded as an aspect of medical care, and that the extent to which disclosure is appropriate should therefore be treated as a matter of clinical judgment, the appropriate standards being set by the medical profession.
75. Since *Sidaway*, however, it has become increasingly clear that the paradigm of the doctor-patient relationship implicit in the speeches in that case has ceased to reflect the reality and complexity of the way in which healthcare services are provided, or the way in which the providers and recipients of such services view their relationship. One development which is particularly significant in the present context is that patients are now widely regarded as persons holding rights, rather than as the passive recipients of the care of the medical profession. They are also widely treated as consumers exercising choices: a viewpoint which has underpinned some of the developments in the provision of healthcare services. In addition, a wider range of healthcare professionals now provide treatment and advice of one kind or another to members of the public, either as individuals, or as members of a team drawn from different professional backgrounds (with the consequence that, although this judgment

57 *Bolam v Friern Hospital Management Committee* [1957] 2 All ER 118.

58 [2015] UKSC 11, para 87.

is concerned particularly with doctors, it is also relevant, *mutatis mutandis*, to other healthcare providers). The treatment which they can offer is now understood to depend not only upon their clinical judgment, but upon bureaucratic decisions as to such matters as resource allocation, cost-containment and hospital administration: decisions which are taken by non-medical professionals. Such decisions are generally understood within a framework of institutional rather than personal responsibilities, and are in principle susceptible to challenge under public law rather than, or in addition to, the law of delict or tort.

76. Other changes in society, and in the provision of healthcare services, should also be borne in mind. One which is particularly relevant in the present context is that it has become far easier, and far more common, for members of the public to obtain information about symptoms, investigations, treatment options, risks and side-effects via such media as the internet (where, although the information available is of variable quality, reliable sources of information can readily be found), patient support groups, and leaflets issued by healthcare institutions. The labelling of pharmaceutical products and the provision of information sheets is a further example, which is of particular significance because it is required by laws premised on the ability of the citizen to comprehend the information provided. It would therefore be a mistake to view patients as uninformed, incapable of understanding medical matters, or wholly dependent upon a flow of information from doctors. The idea that patients were medically uninformed and incapable of understanding medical matters was always a questionable generalisation, as Lord Diplock implicitly acknowledged by making an exception for highly educated men of experience. To make it the default assumption on which the law is to be based is now manifestly untenable.
77. These developments in society are reflected in professional practice. The court has been referred in particular to the guidance given to doctors by the General Medical Council, who participated as interveners in the present appeal. One of the documents currently in force (*Good Medical Practice* (2013)) states, under the heading “The duties of a doctor registered with the General Medical Council”:

“Work in partnership with patients. Listen to, and respond to, their concerns and preferences. Give patients the information they want or need in a way they can understand. Respect patients’ right to reach decisions with you about their treatment and care.”

78. Another current document (*Consent: patients and doctors making decisions together* (2008)) describes a basic model of partnership between doctor and patient:
- “The doctor explains the options to the patient, setting out the potential benefits, risks, burdens and side effects of each option, including the option to have no treatment. The doctor may recommend a particular option which they believe to be best for the patient, but they must not put pressure on the patient to accept their advice. The patient weighs up the potential benefits, risks and burdens of the various options as well as any non-clinical issues that are relevant to them. The patient decides whether to accept any of the options and, if so, which one.” (para 5)
- In relation to risks, in particular, the document advises that the doctor must tell patients if treatment might result in a serious adverse outcome, even if the risk is very small, and should also tell patients about less serious complications if they occur frequently (para 32). The submissions on behalf of the General Medical Council acknowledged, in relation to these documents, that an approach based upon the informed involvement of patients in their treatment, rather than their being passive and potentially reluctant recipients, can have therapeutic benefits, and is regarded as an integral aspect of professionalism in treatment.
79. Earlier editions of these documents (*Good Medical Practice* (1998), and *Seeking patients’ consent: The ethical considerations* (1998)), in force at the time of the events with which this case is concerned, were broadly to similar effect. No reference was made to them however in the proceedings before the Court of Session.
80. In addition to these developments in society and in medical practice, there have also been developments in the law. Under the stimulus of the Human Rights Act 1998, the courts have become increasingly conscious of the extent to which the common law reflects fundamental values. As Lord Scarman pointed out in *Sidaway’s* case, these include the value of self-determination (see, for

example, *S (An Infant) v S* [1972] AC 24, 43 per Lord Reid; *McCull v Strathclyde Regional Council* 1983 SC 225, 241; *Airedale NHS Trust v Bland* [1993] AC 789, 864 per Lord Goff of Chieveley). As well as underlying aspects of the common law, that value also underlies the right to respect for private life protected by article 8 of the European Convention on Human Rights. The resulting duty to involve the patient in decisions relating to her treatment has been recognised in judgments of the European Court of Human Rights, such as *Glass v United Kingdom* (2004) 39 EHRR 15 and *Tysiac v Poland* (2007) 45 EHRR 42, as well as in a number of decisions of courts in the United Kingdom. The same value is also reflected more specifically in other international instruments: see, in particular, article 5 of the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, concluded by the member states of the Council of Europe, other states and the European Community at Oviedo on 4 April 1997.

81. The social and legal developments which we have mentioned point away from a model of the relationship between the doctor and the patient based upon medical paternalism. They also point away from a model based upon a view of the patient as being entirely dependent on information provided by the doctor. What they point towards is an approach to the law which, instead of treating patients as placing themselves in the hands of their doctors (and then being prone to sue their doctors in the event of a disappointing outcome), treats them so far as possible as adults who are capable of understanding that medical treatment is uncertain of success and may involve risks, accepting responsibility for the taking of risks affecting their own lives, and living with the consequences of their choices.
82. In the law of negligence, this approach entails a duty on the part of doctors to take reasonable care to ensure that a patient is aware of material risks of injury that are inherent in treatment. This can be understood, within the traditional framework of negligence, as a duty of care to avoid exposing a person to a risk of injury which she would otherwise have avoided, but it is also the counterpart of the patient's entitlement to decide whether or not to incur that risk.

After *Montgomery*, it seems that clinical practice will need to be modified so that greater care and attention is given to informing patients of the risks associated with particular courses of treatment. It does not follow from this that big biobanks have a duty to take reasonable care to ensure that participants are aware of material risks revealed by researchers using the resource. Even so, after *Montgomery*, the odds that a court might hold that a biobank has such a duty must have shortened significantly.

Causation and 'loss of chance'

In order to succeed in an action in negligence a participant would have to show not just that a biobank breached their duty of care but also that this breach caused damage. Any damage resulting from withholding information from participants is likely to be based in a claim for 'loss of a chance'. The UK House of Lords in *Gregg v Scott*⁵⁹ rejected the argument that someone whose chances of surviving non-Hodgkins Lymphoma were reduced from 42% to 25% by a delay in diagnosis could recover damages. The Courts followed the reasoning of an earlier case, *Hotson v East Berkshire Area Health Authority*⁶⁰, and found that in order to recover in damages the claimant would have to show that their chance of recovery was over 50% in order to establish that on the balance of probabilities they have suffered a loss that is actionable. This means that in order for a participant to be successful in an action in negligence they would have to show that the information withheld from them reduced their prospects of survival from over 50% to below 50%.

Clearly, the over 50% principle creates a serious obstacle to a claim and, for some time, there has been a counter-current of legal authority that seeks to be more claimant-friendly. The idea here is to compensate claimants where the defendant's negligent act or omission has heightened a particular risk of harm even though it cannot be established precisely how material a contribution this has made to the harm that eventuates.⁶¹ In *Montgomery*, this counter-current was pleaded in support of the claim. However, because the Supreme Court held that, had she been advised of the risk of a natural vaginal delivery, the claimant would have opted for a CS, causation was made out on the strict over 50% test and it was not necessary for the court to take a view on the more claimant-friendly

59 [2005] 2 WLR 268.

60 [1987] 2 All ER 909.

61 Notably, see *Chester v Afshar* [2004] UKHL 41.

line of authority. After *Montgomery*, there is no doubt that the legal climate is more patient-centred, but it is moot whether it is also more claimant-friendly with regard to the requirement of causation.

Taking stock

Following the recent decisions in the *St George's Healthcare NHS Trust* case and in *Montgomery*, what are we to make of the legal position? First, we assume that there is no question of a biobank having a duty to take reasonable care to look for HRFs; the question only arises where an HRF 'happens to be found'. Secondly, there is a substantial body of precedents, to which the *St George's Healthcare NHS Trust* case is the latest addition, that holds that there is no duty to take positive steps to alert others to a risk to their health and well-being or to prevent the risk eventuating – for example, the fact that a barman happens to notice that I have had too much to drink does not put them under a legal duty to refuse to serve me another drink.⁶² Thirdly, however, *Montgomery* looks like a ground-breaking decision that prioritises the right of persons to make informed health care choices. While it does not follow in a clear-cut way that participants have a right to the return of HRFs, *Montgomery* certainly implies that consent (whether specific or broad) to any feedback policy would need to be fully informed in order to be valid – after *Montgomery*, consent to a policy without any information about the likelihood of HRFs, the severity of possible conditions, and so on, would seem to be problematic. Fourthly, if in fact it is held that *Montgomery* entails that biobank participants have a prima facie right to the return of HRFs, the right might be overridden by more compelling considerations. Confidentiality is such a consideration but it is unlikely to be relevant in the context of biobanks. Most importantly, after *Montgomery*, a biobank would seem to be on weak ground if it argued, in a paternalistic way, that it had not disclosed HRFs because it judged that they would do more harm than good to participants. Fifthly, one of the persistent themes in the jurisprudence is that it is undesirable to divert doctors from treating patients. Indeed, in the *St George's Healthcare NHS Trust* case, in the context of confidential information, this is one of the nine reasons set against recognising a duty. Thus:

Doctors receive a very great deal of confidential information. It would be burdensome to place on them a duty to consider whether any of it needs to be disclosed to third parties. The time and resources committed to this will be a distraction from treating patients.⁶³

Quite possibly, if biobanks cannot (after *Montgomery*) plead paternalistic reasons for withholding HRFs, the best argument would be that there are public interest considerations that support investment in health research projects and, concomitantly, that militate against taking researchers away from their research activities. This is not to deny that participants have a prima facie right to be informed (as well as a right not to be informed) but it can be overridden by more compelling rights or public interest considerations. All that said, the legal position in our view remains deeply uncertain.

5 The Human Rights Perspective

Famously, in the landmark decision of *Sidaway v Board of Governors of the Bethlem Royal Hospital and the Maudsley Hospital*,⁶⁴ Lord Scarman remarked that the patient's interest in making his or her own decision 'may be seen as a basic human right protected by the common law'.⁶⁵ This view, as we have seen, finds strong echoes in *Montgomery*. Moreover, in *Montgomery*, we read that '[a] person can of course decide that she does not wish to be informed of risks of injury (just as a person may choose to ignore the information leaflet enclosed with her medicine)'.⁶⁶ However, do existing human rights instruments endorse this view and what can we infer about an entitlement to the return of HRFs from such instruments? What do human rights instruments say about the right to be informed and the right not to be informed?

Perhaps the crispest support for both a right to be informed and a right not to be informed is to be found in Article 10.2 of the Convention on Human Rights and Biomedicine (this article dealing with 'private life and the right to information') according to which:

Everyone is entitled to know any information collected about his or her health. However, the wishes of individuals not to be so informed shall be observed.

The right not to be informed is endorsed by Article 5(c) of the UNESCO Declaration on the Human Genome which states that: "The right of every individual to

62 See *Barrett v Ministry of Defence* [1995] 1 WLR 1217.

63 [2015] EWHC 1394 (QB), para 13.

64 [1985] AC 871.

65 At 882.

66 [2015] UKSC 11, para 85.

decide whether or not to be informed of the results of genetic examination and the resulting consequences should be respected.' To be sure, some might quibble about the meaning of 'collected' in Article 10.2 or make something of the fact that the United Kingdom has not actually signed up to the Convention. Nevertheless, these provisions lend support to the idea that humans, qua humans, owe it to one another to share health-related information; and the idea that there is a right not to be informed seems to be even more strongly supported in these provisions.

In some quarters, human rights are interpreted as a particular articulation of more general rights that humans have, not so much as members of the human species, but simply as agents (that is, beings with a sense of their own interests, who are capable of acting freely and in a purposive way). On this approach, too, it is plausible to think that there is a right to be informed about conditions that threaten an agent's basic well-being as well as a right to waive the benefit of this right; and, arguably, too, there is a right not to be informed.⁶⁷

It might be thought that the right not to know is simply a way of indicating that an agent, who has the right to know, has opted not to know. However, it is arguable that the two rights are conceptually distinct. To illustrate, let us suppose that A, having undergone genetic tests, has information that is relevant to B. This is how the two rights map onto the situation:

- If B has the right to know, A is required to inform B; but B may signal that the requirement is waived – that is, B may give an informed consent that authorises non-disclosure by A.
- If B has the right not to know, A is required not to inform B; but B may signal that the requirement is waived – that is, B may give an informed consent that authorises disclosure by A.

In practice, then, there are two *legitimate* possibilities: the information is disclosed (whether pursuant to B's right to know, or under the authorisation of B's

informed consent [relative to the right not to know]); or the information is not disclosed (whether pursuant to B's right not to know, or under the authorisation of B's informed consent [relative to the right to know]).

Whatever the correct analysis, if we are to take rights seriously, then it seems that we need to reckon with both a right to be informed and a right not to know, rights that are potentially material to the relationship between big biobanks and their rights-holding participants.

6 The Preference and Utility Perspective

There is a growing body of social research on biobank participation. This suggests that the lay public is generally supportive of biobanking, optimistic about its research potential and may be willing to participate. Participants give many reasons for taking part, including altruism, reciprocity and the expectation of personal benefits through new therapies or information, direct feedback of study results and the 'clinical' encounter at enrolment. The major concern for potential participants is the potential for a breach of data security or release of sensitive data to third parties.⁶⁸

In what follows we give some indication of (i) what is known about the preferences of participants with regard to the return of HRFs, (ii) what is known about the impact of returning HRFs to participants, and (iii) what we know about the preferences of parties as to the manner and form in which HRFs are returned.

(i) The preferences and understandings of participants

What do we know about the preferences of participants in relation to the return of HRFs? In a pilot study conducted by Brown and Knight, there are indications that, in certain situations of data collection, reciprocation of individual feedback may be a condition for participation for some individuals. This study⁶⁹ (N=45) was carried out with members of the 1958 birth cohort National Child Development Study who were asked whether they would be willing to take part in an fMRI study. Most (95%) were willing (and 16% had been previously scanned for clinical reasons). While 43% of the participants said they would agree to take part regardless of whether or not they received individual feedback, 41% said they would only do so if they got feedback on all potential problems, and for 11% of the sample, feedback only on potential

67 Deryck Beylveid and Roger Brownsword, 'Research Participants and the Right to be Informed' in Pamela R. Ferguson and Graeme T. Laurie (eds), *Inspiring a Medico-Legal Revolution* (Essays in Honour of Sheila McLean) (Farnham: Ashgate, 2015) 173.

68 Wendy Lipworth *et al* 'Tissue donation to biobanks: a review of sociological studies' (2011) 33 *Sociology of Health & Illness* 792-811; Kelly E Ormond *et al* 'The views of participants in DNA biobanks' 1 (2010) *Journal of Law, Science & Policy* 80-87.

69 Matthew Brown and Helen M Knight, 'Attitudes toward participating in fMRI studies amongst participants in a birth cohort study' (Working Paper 2010/8; Centre for Longitudinal Studies, University of London, 2010).

problems considered to be both serious and treatable. Stated motives for taking part in such a study included contributing to important research, loyalty to the cohort study, as well as the possible opportunity to benefit from early detection of problems, or the reassurance a scan might provide that all is well.

There is other evidence from a USA study⁷⁰ of healthy control subjects who had had experience of participating in neuro imaging research (in medical and non-medical settings) that some participants would wish to know “everything” that is found, i.e. including benign abnormalities. Indeed, 90% of the sample wanted to be informed of abnormalities whether these were i) benign, ii) malignant, but curable, iii) malignant, not curable, or iv) a life threatening emergency.

There are indications from some biobanks that at least some participants see them as, in effect, a health check. This is not surprising as many of the procedures are familiar diagnostic assessments which participants may have experienced in therapeutic settings (e.g. blood pressure measurement, blood tests, MRI and DXA scans). The US study cited above also indicated that 50% of control subjects who had participated in neuro imaging research expected scans to detect abnormalities if these existed, regardless of what had been said in the information given them in the consent process.⁷¹

We can learn more about the understanding of participants from the Genome Ethics study, based at the Wellcome Trust Sanger Institute in the UK, which used a cross-sectional web-based survey to investigate the attitudes of 6944 individuals from 75 countries towards returning IFs from genomic research. Participants included four relevant stakeholder groups: 4961 members of the public, 533 genetic health professionals, 843 non-genetic

health professionals and 607 genomic researchers. The study found that ‘treatability and perceived utility of incidental results were deemed important with 98% of stakeholders personally interested in learning about preventable life-threatening conditions.’⁷² They also noted, however, that while there was a generic interest in receiving genomic information, stakeholders did not expect researchers to opportunistically screen for IFs in the research setting, recognising that the practical burden of doing so could compromise the ability to address the primary research question.

Do we know why participants prefer the return of HRFs? A review by Shalowitz and Miller reported on nine studies that assessed participants’ reasons for wanting aggregate and individual research results. Reasons included clinical significance (e.g. treatment, prevention, or understanding of a disease) for self or relatives, respect for participants in research or a ‘right’ to receive results and raising public awareness of research.⁷³

(ii) Impacts of receiving feedback

Work⁷⁴ has been carried out with a sample of the Scottish Twenty- 07 study participants who received a letter containing their body mass index (BMI), body fat percentage, cholesterol and glycated haemoglobin results.

“Expectations of, and response to, the feedback of their individual results varied. Whilst half of the participants were on the whole ‘pleased’ with their results or held neutral views, half reported negative responses such as ‘shock’ or ‘concern’, particularly in relation to the weight-related results. Participants who were overweight and obese used the most negative language about their results, with some being quite distressed and reporting feelings of powerlessness, low self-image and anxiety over future health. Nevertheless, some people reported having implemented lifestyle changes in direct response to the feedback, result in significant weight loss and/or dietary improvements. Others reported being motivated to change their behaviour. Age and gender differences were apparent in these narratives of behaviour change.”

Conclusions

The potential harm caused to some participants may be balanced against the benefit to others. More evaluation of the impact of the format, content and means of feedback of research findings in non-trial studies is required given the growing ethical imperative to inform participants of their results.”⁷⁵

70 Matthew P Kirkschen *et al* ‘Subject expectations in neuro imaging research’ (2006) 23 *J. Magnetic Resonance Imaging* 205-209.

71 Matthew P Kirkschen *et al* ‘Subject expectations in neuro imaging research’ (2006) 23 *J. Magnetic Resonance Imaging* 205-209.

72 Anna Middleton *et al* ‘Attitudes of nearly 7000 health professionals, genomic researchers and publics toward the return of incidental results from sequencing research’ *European Journal of Human Genetics* advance online publication 29 April 2015; doi: 10.1038/ejhg.2015.58.

73 David I Shalowitz and Franklin G Miller ‘Communicating the results of clinical research to participants: attitudes, practices, and future directions’ (2008) *PLoS Med* 5(5): e91.

74 Karen Lorimer *et al* ‘Response to written feedback of clinical data within a longitudinal study: a qualitative study exploring the ethical implications.’ (2011) 11 (10) *BMC Medical Research Methodology*.

There has been a limited amount of research about communicating research findings to participants. Further, it is very difficult to draw many general conclusions from these studies as much may depend on the kinds of research studies involved and the impact of findings depending on characteristics of the participant population (diagnosis, health status, education, etc).⁷⁶

We can learn more from the field of research MRI imaging, where for the best part of a decade, it has been generally regarded as good practice to inform research participants of HRFs. Indeed, a number of units in the UK require participants to receive such feedback, if they wish to take part in the research. And while we know on the basis of reported cases that both benefits and disbenefits can accrue to participants who receive feedback, we lack any systematic reports of the outcomes for research participants. It is uncertain how far research participants may, or may not, benefit from such policies for feedback and without some better evidence about outcomes it is difficult to justify current policies regarding feedback of HRFs in research imaging.⁷⁷

The review by Shalowitz and Miller⁷⁸ was able to identify only one study which looked at the impact of receiving (genetic) findings (in a sample of women who had been diagnosed with breast cancer).⁷⁹ This almost total lack of evidence about outcomes in biobanks for

participants receiving individual feedback of HRFs, undermines the attempt to make evidence-based policy. To develop feedback policies and procedures we need to know more about what participants want and, indeed, what they may expect, as regards different kinds of feedback. Here we need not only to capture broad attitudes but also wishes having regard to the complexities of the validity and utility of information that could be provided. We also need to assess their subjective experience of receiving feedback. Thus, in depth and more deliberative research approaches will be needed.

(iii) Preferences with regard to the manner and form of the return of HRFs

What do we know about the preferences of both biobanks and participants in relation to the manner and form in which HRFs are returned?

Wilson *et al*⁸⁰ surveyed 343 mothers that participated in the Health Outcomes and Measures of the Environment Study about their biomarker feedback preferences and found that preferences for the method of receiving results differed by education level.⁸¹ In the light of this the authors suggest that those offering feedback should reassess using a single format or forum for disclosing results. It should be borne in mind, however, that using differential feedback methods with the same cohort of participants might give rise to equity issues.

Wilson *et al* cite a further study⁸² that compared the effectiveness of in-person feedback to letter/telephone feedback in a genotype disclosure study. This study found letter/telephone feedback to be as effective as in person feedback, as there were no significant differences in recall, satisfaction or understanding of the results between the two groups.

Recently there have been examples of biobanks providing (computer-using) participants with personal protected websites through which they can access their own individual reports⁸³, including links to supporting information to give context to the test results and health risk information. On the positive side, some individuals will welcome this option of e-participation just like some welcome the option of on-line-banking. Moreover, one of the attractions of the use of web or e-mail based systems for the communication of results is that they cost less and are easier to operate for biobanks than letters, or any person to person communication system. Given that costs may be a (justifiable) limiting factor in providing feedback it seems not unreasonable to aim for a 'good enough' communication system rather than a more personalised, ideal system which would require much

75 Karen Lorimer *et al* 'Response to written feedback of clinical data within a longitudinal study: a qualitative study exploring the ethical implications.' (2011) 11 (10) *BMC Medical Research Methodology*, p.2.

76 David I Shalowitz and Franklin G Miller 'Communicating the results of clinical research to participants: attitudes, practices, and future directions' (2008) *PLoS Med* 5(5): e91.

77 The Royal College of Radiologist 'Management of incidental findings detected during research imaging' London: The Royal College of Radiologist, 2011.

78 David I Shalowitz and Franklin G Miller 'Communicating the results of clinical research to participants: attitudes, practices, and future directions' (2008) *PLoS Med* 5(5): e91.

79 Martin Richards *et al* 'Issues of consent and feedback in a genetic epidemiology study of women with breast cancer' (2003) 29 *Journal of Medical Ethics* 93-96.

80 Stephen Wilson *et al* 'Understanding preferences for disclosure of individual biomarker results among participants in a longitudinal birth cohort' (2010) 36 *Journal of Medical Ethics* 736-740.

81 Mothers with less than a college degree preferred in-person feedback of results more often than mothers with some college education or a college degree.

82 Colleen M. McBride *et al* 'Maximizing the motivational impact of feedback of lung cancer susceptibility on smokers' desire to quit' (2000) 5(3) *J Health Commun* 229-241.

83 BBMRI.NL 'MyBiobank app: Pioneering online feedback' (March 2013) 8 *Hub* 2.

more resource from a biobank. Against such positive features, however, if such a system were to be adopted, care should be taken to avoid creating two classes of participants arising from any ‘digital divide’.

Procedures for feedback are widely variable and there is limited systematic research on outcomes for participants which might help to guide practice. The way in which feedback is provided is likely to influence reactions to it. We need outcome research to develop and modify practice so it may become more evidence-based; at present we simply know too little about the impact on participants of receiving various kinds of individualised feedback.

What should we conclude from this limited data? Quite simply, if the preference and utility perspective aspires to operate in an evidence-based way, more evidence is needed.

7 The Paternalistic Perspective

The basic idea of paternalism is that A, assuming responsibility for B’s welfare, speaks for what is in B’s interest and acts accordingly on that judgment. Hence, if A judges that x is not conducive to B’s welfare, A will prevent x and will do so irrespective of B’s judgment as to whether x is in B’s interest. Where A has the knowledge and skill to make reasonable judgments as to B’s welfare, and where B is incapable of making judgments as to what is in their best interest – for example, where A is a competent parent and B is A’s young child – then paternalism may well be justifiable. However, one of the obvious problems with a paternalistic perspective is that it is applied even where B is perfectly capable of judging what is or is not in their own interest. When B is so capable, the fact that A may have special knowledge or expertise is not sufficient.

In *Montgomery*, the line between acceptable and unacceptable medical paternalism is drawn in terms of ‘a fundamental distinction between, on the one hand, the doctor’s role when considering possible investigatory or treatment options and, on the other, her role in discussing with the patient any recommended treatment and possible alternatives, and the risks of injury which may be involved.’⁸⁴

Then, we read:

The former role is an exercise of professional skill and judgment: what risks of injury are involved in an operation, for example, is a matter falling within the expertise of members of the medical profession. But it is a *non sequitur* to conclude that the question whether a risk of injury, or the availability of an alternative form of treatment, ought to be discussed with the patient is also a matter of purely professional judgment. The doctor’s advisory role cannot be regarded as solely an exercise of medical skill without leaving out of account the patient’s entitlement to decide on the risks to her health which she is willing to run (a decision which may be influenced by non-medical considerations). Responsibility for determining the nature and extent of a person’s rights rests with the courts, not with the medical professions.⁸⁵

Where the court determines, as it does in *Montgomery*, that it is the patient’s right to make their own informed choices about where their best interest lies, then it is for the patient, not for the doctor, to assume responsibility for the patient’s welfare. The paternalistic perspective is overreached in such circumstances.

Applying this analysis to the principles that should guide a biobank’s position on the return of HRFs, it is clear that a constellation of ideas that draw on paternalism – such as third-person assessments of benefit, risk, harm, and best interests – are highly problematic. What *Montgomery* implies is that the human rights perspective should rule and that the principles relating to respect, reasonable expectation, and consent (as an aspect of a will theory of rights) should prevail.⁸⁶

84 [2015] UKSC 11, para 82.

85 [2015] UKSC 11, para 83.

86 Deryck Beylveid and Roger Brownsword, *Consent in the Law* (Oxford: Hart, 2007).

8 The Practice-Guided Perspective

The essence of the practice-guided perspective is not to lead practice but to fall in line with it. In order to do this, it is necessary to have a sense of the landscape of biobanking practice.

Traditionally, biobanks have adopted a policy of not providing feedback of HRFs; and, as the samples in Annex A indicate, many biobanks continue to open their protocols with a declaration that they will not normally feedback research findings to individual participants (although routine measurements at enrolment might well be returned). However, the direction of travel seems to be towards offering HRFs in certain circumstances. For example, the US Kaiser Permanente Research Program on Genes, Environment and Health will offer results of research if they believe them to be 'of substantial medical importance' to the participant; and the Swedish biobank, LifeGene, may provide 'findings of new biomarkers implicating a very high risk of a preventable and serious disease' if corroborated and if relevant medical expertise finds this defensible. But, how representative are these cases? It is important to know because, where biobanks are guided by one another's practice, a change by some biobanks towards returning some HRFs will encourage others to do so.

Drawing on the sample of feedback policies in Annex A, what can we deduce about biobanking practice? We suggest that three features stand out as follows.

First, a significant number of biobanks do make some provision for the return of HRFs. Whether this is now the majority or still a minority, we do not know. However, a practice-guided perspective could encourage a biobank to adopt a position either way.

Secondly, where biobanks give their reasons for deciding for or against the return of HRFs, there are often prominent references to risk/benefit considerations in conjunction with the consent (qua preferences) of participants, suggesting a perspective that is either paternalistic or utilitarian.

Thirdly, there are few examples of biobanks majoring on the idea that participants have a right to the return of HRFs, or the right not to be informed. However, there is a striking and rare instance of explicit rights thinking in the case of the Estonian Genome Project; and LifeGene, too, relies to some extent on a rights-focused perspective.

Given this limited support for a rights-based approach, a biobank taking a practice-guided perspective would be unlikely to adopt a feedback position that reflected a focus on the rights of participants. However, if

our reading of *Montgomery* is correct, a biobank that looked to practice to justify either a no feedback policy or a paternalistic position based on risk/benefit analysis would be vulnerable to a legal challenge. Once the legal position becomes clear, biobanks need to take their steer from the law not from the practice of other biobanks.

9 Conclusion

The literature confirms that the ethics and practice of returning HRFs are complex and contested. Nevertheless, we detect a growing consensus on a number of points – in particular, that big biobanks have an obligation to 'determine and make clear to research participants whether [HRFs] will or will not be offered back to the participants';⁸⁷ that, whatever the biobank's policy on feedback, reasons should be given for the adoption of the particular position; and that the determination of a biobank's position in relation to the return of HRFs should follow consideration of a set of generally agreed guiding principles. In this context, our principal conclusions, as prefigured in our introductory remarks, can be expressed in the form of three questions and responses as follows.

First, how well are big biobanks doing in relation to the ethics and governance of HRFs? Without doubt, there has been a welcome step change in the practice of biobanks in the way that they deliberate about the ethics of returning HRFs, and in the way that they communicate and explain their feedback policies. Nevertheless, the guiding principles suggested by best practice give biobanks considerable leeway in adopting and justifying their feedback position. Biobank A and Biobank B can have diametrically opposed feedback policies; they can appeal to the same set of foreground principles to justify their positions (albeit different principles within the set); and they can both plausibly claim to be examples of best practice.

Secondly, could biobanks do any better and would it be desirable to try to do so? We have suggested that greater transparency in the articulation and explanation of biobank positions would be achieved if the key background perspectives to which biobanks orientate their feedback policies were drawn out. This

87 Susan Wolf *et al* 'Managing incidental findings and research results in genomic research involving biobanks and archived data sets' (2012) 14 *Genetics in Medicine* 361-384.

Annex A: Feedback policies of a sample of biobanks

would mean that the background perspectives to which biobanks tend to default would be brought into the open and exposed to critical scrutiny. However, that would be no bad thing.

Thirdly, what is the likely impact of *Montgomery*, in relation the law concerning the return of HRFs? We have suggested that the import of *Montgomery* is that both the background orienting perspective for big biobanks and the principles that guide best practice need to reflect far more explicitly the idea that participants have rights; and that the ethic that shapes biobank practice is appropriately rights-focused. If this is correct, while biobanks have made great strides in taking up principled positions in relation to the return of HRFs, it seems that the principles that they often prioritise draw on a paternalistic perspective that is simply out of step with a culture of respect for the rights of patients and participants. If our reading of *Montgomery* is on the right track, then big biobanks that have failed to adjust their perspective might find that they are backing the wrong ethical principles. Whether or not there will be questions, too, about their legal compliance remains to be seen. English law, as the *St George's Healthcare NHS Trust* case confirms, is reluctant to recognise positive duties and especially so where the duty bearers would be diverted from doing work that is in the public interest.

- 1 ALSPAC
- 2 UK10K: Rare genetic variants in health and disease
- 3 1958 birth cohort
- 4 CARTaGENE
- 5 Framingham Heart Study
- 6 Estonian Genome Project
- 7 Generation Scotland
- 8 TwinsUK
- 9 Kaiser Permanente Research Program on Genes, Environment and Health
- 10 LifeGene
- 11 NuGene
- 12 String of Pearls
- 13 Western Australia DNA Bank
- 14 International Cancer Genome Consortium
- 15 West of Scotland Twenty-07 Study
- 16 Qatar Biobank
- 17 Genomics England/100,000 Genomes Project
- 18 UK Biobank

1 ALSPAC

“Policy regarding disclosure of biomedical information to participants⁸⁸

The policy is that information shall not, as a general rule, be disclosed to participants.

This general policy should only be set aside when it is reasonably certain that the benefits of disclosure clearly outweigh any possible risks to the participants or their families. This in turn will arise when three conditions are met:

1. That an item of data gives clear, unequivocal information of an existing or future health problem.
2. That the health problem identified is amenable to treatment of proven benefit
3. That the participant has indicated beforehand that they wish to be informed if such a problem is identified.

A number of principles have informed the discussions of the Committee:

- Individuals have consented to participate in the study on the clear understanding that all measures are for research purposes only and not to inform decisions about their health. To emphasise this, it is often stated explicitly in the information given to participants.
- As a corollary, it is frequently repeated that the tests that participants undergo are not a check on their health, and that if participants are worried they should go to their own doctors.
- The relationship between researcher and participant differs from that between doctor and patient. Crucially the duty of care is different. The primary concern of a researcher is not to the health of a participant but to acquire information for the benefit of humankind.
- Disclosing information will not necessarily be beneficial to participants. Individuals will differ in their approach to receiving information about themselves, and for some it could result in negative, unforeseen consequences.
- In practice, some measurements are undertaken in order to define more precisely their relationship to future health problems. In this instance the risk to any individual cannot be known, and therefore the information should not be divulged to them.

This policy should be applied in all circumstances, including:

- All biophysical measurements, whether they are the primary purpose of a study or incidental findings identified in the course of a study
- All questionnaire results that have been administered to identify health problems. Answering questions does not equate to knowing the outcome of the whole questionnaire, and therefore participants do not already know or understand their own data.
- The results of tests where analyses take place some time after the samples were taken. This arises if biological samples are analysed in batches after they have been taken. If it is thought that feedback of abnormal results will be important and necessary, the Committee may try to ensure that such delays are minimised.
- In particular, tests to identify either specific genes or more extensive genetic sequencing.

The only circumstances where this does not apply is where measurements have been taken in the presence of the participants, where the information would have to be concealed from the participants, such as height, weight, blood pressure, etc. This exception is made more on practical grounds than from any application of principle.

This policy does not in any way countermand the long standing practice that ALSPAC provides the results of completed studies to all participants as soon as possible. This is usually done in the form of a newsletter.

There is one particular difficulty that can be predicted. This arises when advances in technology or in the understanding of disease processes so that important measurements can be made on biological specimens taken some time before. It is in the nature of a long-term study like ALSPAC that such circumstances will inevitably arise. Because participants could not have been asked at the time that the specimens were taken, the general principle would be not to disclose the information. This might be overridden if it was felt sufficiently important to seek further consent from participants; or if the condition identified were so severe that the argument for disclosing the information outweighed other considerations.

⁸⁸ Information taken from: www.bristol.ac.uk/alspac/researchers/data-access/ethics/ (accessed June 2015).

Duty of informing participants. In line with its previous conclusion, the Committee felt that the decision whether to inform individuals should be taken by the Committee, drawing on advice from clinical experts. This would keep such decisions independent of the researchers and would be consistent with the Committee's role of protecting the interests of participants.

David Jewell

Chair, ALSPAC Ethics & Law Committee

March 2011"

2 UK10K: Rare genetic variants in health and disease

Extract from the UK10K Ethical Governance Framework⁸⁹, drafted by the Ethical Advisory Group of the UK10K project (Version 21, 14th September 2010):⁹⁰

"Feedback to Participants

In most cases participants will be able to access the research findings of the UK10K project through the UK10K website (www.uk10k.org) where a lay description of the project, media releases, and publications in peer-reviewed scientific journals can be found. As a general rule, the UK10K study will not feedback to participants their genome sequence data, either as a matter of course or on request by the participant. This is because research data produced by the UK10K project is not of a clinical diagnostic standard. Ten percent of the UK10K project comprises studies of patients with rare genetic diseases, many of whom have specifically consented to have pertinent diagnostic data fed-back to them. These individual research studies have already established robust management pathways for validating potentially diagnostic research data to diagnostic standards prior to reporting back to the patient.

Findings of clinical significance

The investigators of the UK10K project have an obligation to establish robust management processes for handling potential clinically significant findings should they arise, but do not have an obligation to search for such findings. Management processes to facilitate this will be agreed and established prior to data generation commencing and must have the approval of the

relevant authorities, such as a research ethics committee.

There are many REC-approved precedents within the UK for not feeding back any individual genetic research findings to participants. However, these are typically situations where the results from the study are expected to have little, or no predictive value to individuals.

A small minority of the genetic variants identified in the UK10K study may be 'clinically significant', which we define as those variants that contribute to the current disease status or alter assessment of the future disease risk of the research participant. Of all the ethical issues raised by the UK10K project, we consider the issue of feedback to participants of genetic research findings of potential clinical significance to represent the most substantive risk of divergence between the existing consents and the National Research Ethics Service (NRES) guidelines on informed consent. Below we expand on the legal and ethical background to this issue and the policies and guidelines we have established for managing this issue.

We distinguish between two classes of clinically significant findings: those that pertain to the disease being researched in each project, which we term '*pertinent findings*' (PFs), and those that relate to other diseases outside of the original research objectives, which we term '*incidental findings*' (IFs). 'Incidental', in this context, means incidental to the original aims of the research study, and are therefore unforeseen at the time that participants give consent. 'Incidental' does not imply that the evidence for disease causality is weaker, or that the associated disease is less severe. Given the nature of the data being generated by the UK10K project, the potential for identifying potential IFs is considerably increased compared to previous genetic research projects. The assessment criteria that apply to PFs and IFs are slightly different, although the management pathways are the same.

There are many REC-approved precedents within the UK for genetic research studies feeding back confirmed clinically significant findings to the patient that pertain to their existing disease status (PFs). Among some of the studies participating in the UK10K project, some patients have explicitly consented to feedback of PFs, and there are pre-existing management pathways for confirming the analytical and clinical validity of research findings relevant to a specific disease and

89 Information taken from: www.uk10k.org/assets/EF_UK10K_v21.pdf (accessed June 2015).

90 Green & bold = policies, purple & italics = guidelines.

communication of these findings to the patient. We regard that ethically robust feedback to participants of findings that pertain to the current disease status of the participant (Pertinent Findings – PFs) is a desirable benefit of the UK10K project.

We are unaware of any REC-approved precedents within the UK for genetic research studies feeding back confirmed ‘incidental findings’.

The duty of care owed by a researcher towards a research participant regarding the feedback of clinically significant findings is not well established in UK law, although clinicians do have a legal duty of care for their patients. Many of the collaborating studies in UK10K involve principal investigators who may have a dual role as a treating clinician and as a researcher. Within the project, there are different types of principal investigators: non-clinical custodians of population cohorts; clinical custodians of population cohorts; clinical custodians of patient collections from different recruiting physicians; and clinical custodians of patient collections who are themselves recruiting physicians for some or all patients.

There are no national guidelines from the National Research Ethics Service (NRES) regarding the feedback of clinically significant findings in genetic research, other than that during the consent process information should be provided about any procedures for feedback of “*individually significant*” information, and that any such feedback should be explicitly consented to. Consequently, it is not straight-forward to unambiguously establish the standards that ought to be applied when considering the feedback of clinically significant findings from a genetic research study such as the UK10K project. Feedback is only possible if an individual can be identified and it is possible to contact them.

Our understanding of which genetic variants are clinically significant is ever-changing. Moreover, in the context of a project whose explicit objective is to make data available to other researchers, in principle, potential clinically significant findings might be identified through analyses undertaken by non-UK10K researchers accessing the data through managed data access mechanisms, whom we term collectively ‘secondary researchers’. An open commitment to re-evaluate *ad infinitum* genetic data from a research participant to identify clinically significant findings is simply not sustainable.

In the context of a large project comprising many different principal investigators, such as the UK10K project, the role of the project is to develop consensually a framework of principles to achieve

consistency and equality of consideration across the project for considering the feedback of clinically significant findings. Therefore, there is not a single approach for discharging this moral duty should it arise as different circumstances may exist for different participant collections and principal investigators.

- *If a principal investigator decides that feedback of findings of clinical significance is appropriate then this must have the consent of the research participant and approval by a research ethics committee. All communications of findings of clinical significance carry a risk of causing unnecessary harm to the research participant and their families. Thus the principal investigator must balance the potential risks and benefits of feeding back clinically significant information and appropriate management pathways must be in place.*
- *If a principal investigator decides that feedback of findings of clinical significance is appropriate, and yet a potential participant has requested no further contact with the research team during the consent process, then the participants ‘right not to know’ should be respected, and their participation should not be disallowed on the grounds that feedback of findings of clinical significance is not possible.*
- *If a principal investigator decides that it is not appropriate to feedback any genetic findings of clinical relevance, this course of action must have research ethics committee approval, and, where possible, and if the participant has consented to further contact, then the participant should be contacted and informed that no feedback will occur.*

Assessment Criteria

Feedback of findings of clinical significance from a research study, whether a pertinent or incidental finding, is only ethically sound if:

- 1. The participant has explicitly consented to the feedback of that specific class of finding (i.e. pertinent and/or incidental findings of specified clinical utility), and has been given an opportunity to exercise their ‘right not to know’ and yet still participate in the research.**
- 2. The analytical validity of the research finding is established in an independent sample from the patient by a CPA-accredited laboratory.**
- 3. The clinical validity of the research finding must be of equivalent robustness to information fed back from a clinical diagnostic test.**

4. Mechanisms exist for the appropriate clinical management of feedback to participants.

Feedback of PFs will not be applicable to participants who have not been recruited for research on the basis of a specified clinical condition. Therefore for the UK10K project, the feedback of pertinent findings is applicable to disease-focused studies, and not to the cohort studies.

Given the lack of precedents for the feedback of IFs from genetic research and the relative lack of research on the impact of feedback of IFs from genetic research, currently, we regard that it would only be ethical to consider the feedback of IFs of the greatest clinical validity and clinical utility, in other words, where there is an unambiguously predictive relationship between the genotype and disease, and a clinical intervention to mitigate the disease risk is available, and the benefits of that clinical intervention unambiguously outweigh the harms. If a UK10K principal investigator applies for and obtains research ethics committee approval for feedback of IFs, the Ethical Advisory Group will work with the principal investigator (and consult with appropriately qualified experts) to implement this assessment of clinical validity and clinical utility for potential IFs. Given the current lack of precedents and relevant research, we expect that best practice for management of IFs may change, and accordingly this policy will be subject to review.

Research findings from the UK10K project will not be of the same standard as clinical diagnostic tests. For example, sample tracking in a research setting is not infallible, which raises the very real risk of causing harm by feeding back information to the wrong person. It is not ethically sound to feedback research findings without having established the analytical validity (accuracy of the genotype in the participant) and clinical validity (the accuracy of the genotype in identifying or predicting a particular clinical condition) of the research finding.

- *Assuring that a research finding is of the same quality of information as provided by a clinical diagnostic test, requires that the analytical validity and the clinical validity of the finding can be confirmed to the same standards as are applied to clinical diagnostic testing.*
- *Assuring that a research finding is of the same analytical validity as provided by a clinical diagnostic test is best accomplished by confirmatory testing of an independent sample that has been handled, stored and tested in a laboratory that has been accredited*

by Clinical Pathology Accreditation Ltd (CPA-accredited). Such an independent sample may require obtaining a fresh sample from the participant, or using a previously taken sample that has been handled exclusively within a CPA-accredited environment, allied with relevant research and clinical expertise of the disease.

- *Prior to analysis by the CPA-accredited laboratory it is desirable for the researcher to verify the findings in an independent experiment so as to minimize unnecessary workload for CPA-accredited laboratories.*
- *Assuring that a research finding in a participant is clinically valid requires that variants of the same type in the same gene have been unambiguously identified as being pathogenic in a peer-reviewed journal. This assessment of clinical validity is best undertaken by those whose professional duty is to make such judgements, typically in a clinical diagnostic laboratory setting.*
- *Participation in research should not be necessarily precluded if a participant is not contactable, due to the obligation to make best use of a research donation by the participant. However, inclusion of such a participant may rule out establishing the analytical validity of a research finding and/or feeding back findings of clinical significance if it is not possible to contact them.*

Management Pathways

UK10K researchers who identify a research finding of potential clinical significance should attempt to identify whether the participant comes from a study in which at least some participants have consented for feedback for the appropriate clinically significant finding (i.e. PF or IF) before contacting the relevant principal investigator, through the UK10K Management Committee, if necessary.

It is the responsibility of the UK10K project management to ensure that a research finding of potential clinical significance (PF or IF) in a research participant identified by UK10K researchers is passed on to the appropriate principal investigator.

If a REC has approved the feedback of clinically significant findings (PFs and/or IFs) and the patient has consented to the feedback of those findings and the assessment criteria have been met, it is the responsibility of the principal

investigator to feedback clinically significant findings according to the REC-approved management pathway, which may differ between studies. This is only possible if participants can be identified and they can be contacted.

Secondary researchers who, having accessed UK10K data through managed data access mechanisms, may identify a research finding of potential clinical significance in a research participant might attempt to contact the relevant principal investigator directly. The name and contact details of the principal investigator for a specified study collection will be made available to facilitate this. If it is not possible to contact the principal investigator directly, a secondary researcher might choose to contact other UK10K project members or the independent Data Access Committee. The UK10K project member or the Data Access Committee member should pass on the information to the relevant principal investigator, via the UK10K Management Committee if necessary.”

3 1958 birth cohort⁹¹

The following extracts are taken from the National Child Development Study: 2002-3 information leaflet⁹². The assessments involved the following: height, weight and other body measures; blood pressure; lung function; eyesight tests; hearing tests; mental wellbeing questionnaire; saliva sample and blood sample.

“The nurse will take a small amount of blood (no more than five teaspoonfuls) from your arm, which is then posted to a laboratory for tests of cholesterol and glycosylated haemoglobin, two substances in the blood which are related to hardening of the arteries (atheroma). We shall inform you if either of these tests is high enough to need medical attention. With the blood sample we are also planning to measure substances related to blood clotting. We shall also test for an antibody (IgE) which is involved in allergies to things like grass pollen and house dust mites.”

“Letting you know your results

At the end of the visit, the nurse will give you a written summary of the measurements she has made on the day. This will not include laboratory tests, nor a detailed medical interpretation of the results. After a few weeks, you will receive a “thank-you” letter including fuller feedback. We will not send any information to your doctor (GP) without your permission, but if you agree, the results of all your measurements and laboratory tests will be sent to your doctor in a separate letter.”

4 CARTaGENE

Phase A brochure for participants⁹³

“Communication of results to participants

Only the results of the physical measures will be given to participants. These results do not amount to a medical diagnosis.

However, if any of the results of the physical measurements of a participant are not within the generally acceptable range, the nurse will inform the participant and recommend that (s)he consults a medical professional. If the result is such that it requires immediate intervention, the participant will be referred to an on-call doctor at the healthcare facility where the appointment is taking place.

After the appointment, if the laboratory results of the analyses of the samples from a participant are not within the generally accepted range and reveal a life-threatening condition for the participant, these results will be communicated to the coordinator responsible for the CARTaGENE Project at the healthcare facility where the appointment took place. A physician of the healthcare facility where the participant has taken his appointment will then communicate with the participant to inform him of the results and to give the necessary explanations. This will be done within seven (7) days of the appointment.

No results from future research projects using data or samples will be communicated to participants of CARTaGENE.”

5 Framingham Heart Study⁹⁴

A. Framingham Heart Study Overarching Philosophy for Adding New Individual results Reports

Our overarching philosophy is to report results back to physicians and participants that are clinically actionable. That is, if there is an acceptable clinical guideline to follow, results are reported. In areas where results are not clinically actionable, in general we do

91 The 1958 cohort has considered the issue of feedback in relation to MRI see Martin Richards (2011) ‘An ethical review of the use of functional MRI and DNA analysis in birth cohort studies’ CLS Working Paper 2011/4. London: Centre for Longitudinal Studies.

92 Information taken from: <http://www.b58cgene.sgul.ac.uk/maininfo.pdf> (accessed April 2013).

93 Information taken from: <http://cartagene.qc.ca/en/documents> (accessed June 2015).

94 This information was provided by FHS colleagues in 2012 and reflects practice at that time.

not report results to our participants. This principle has been reinforced by feedback we regularly receive from the personal primary care physicians for our participants to whom we send test results.

We recognize that these fields are in constant evolution, and that we need to reassess our current reporting strategies on an ongoing basis. We also need a mechanism to assess new technologies that are introduced into our study. The next section provides a detailed explanation for our process to add new individual result reports. Finally, we demonstrate how these principles apply to 4 areas of results reporting: 1) our clinic; 2) biomarkers; 3) imaging; 4) genetics and genomics.

B. Framingham Heart Study Process for Adding New Individual Result Reports

The Framingham Heart Study has been providing some individual research results to the participants and to their personal physicians for decades. Over the years, many new measurements have been ascertained, and some of these are considered to be of possible benefit to the welfare of the participants. The following procedure has been developed by which FHS individual research results can be evaluated for reporting to the participants and to their physicians.

- A Principal Investigator (PI) from the core FHS examination or from an FHS ancillary identifies a new result report that may benefit some or all participants. In general, PI's are asked to address whether or not reporting is warranted for all research tests that are conducted.
- The PI presents the new result description, justification for reporting to individuals, and draft of the report letter to the FHS Executive Committee.
- If further expert advice is needed, the FHS Executive Committee may seek expertise of the following experts or committees:
 - FHS Genetics Reporting Advisory Committee for expert advice on current genetic findings.
 - Special Experts in the disease or condition of interest.
- The FHS Executive Committee reviews the presentation and, when applicable, expert advice, and if in agreement, presents the proposal to the following committees:
 - FHS Ethics Advisory Committee for feedback from selected participants, local physicians, ethicists and genetic counselors.

- The FHS results reporting committee (a sub-committee of the executive committee) for reviewing and summarizing the accumulated information and feed-back.
- OSMB (Review and Approval Required)
- BUMC IRB (Review and Approval Required)

After a plan for adding a new report is approved, the FHS Executive Committee makes arrangements for adding the new result to its reporting program. Results may be reported either as routine reports to all study participants, as alert referral reports with specific thresholds, or as incidental findings depending on the characteristics of the type of measurement. Individual consent history with regard to notification is in an FHS data set.

C. Results Reporting in the FHS Clinic

Referral and Notification of Participants Regarding Exam Findings: Offspring Exam 9 and Omni Group 1, Exam 4

Two physicians staff the FHS research clinic during the participant examination. The FHS clinic physician reviews with each participant any significant medical history or physical findings identified during the examination. A referral tracking form is completed for each participant documenting the need for further medical evaluation. The reason for further evaluation and the method used to inform the participant and the participant's personal physician are documented on the form. Laboratory results are not available at the time of the clinic visit. Abnormal results are faxed to the participant's personal physician's office. The lab staff calls the office to alert the staff that a fax is coming.

A report of the exam visit is routinely sent to all participants and the participants' personal physicians after the clinic visit.

Participant clinic visit report:

- Lay written report of any clinical finding requiring follow-up with the personal physician
- Results of lipid profile and glucose
- Physical activity monitor report
- Additional reports from ancillary studies
- ECG Wallet Card

Participant’s personal physician/healthcare provider clinic visit report:

- Physician obtained resting blood pressure measurements
- ECG interpretation along with copy of the 12-lead ECG
- Summary of significant medical history and physical exam findings
- Results of lipid profile, creatinine, eGFR, glucose, hemoglobin A1c, CBC, liver function tests, calcium, phosphorus, CRP
- Pulmonary function testing report
- Ankle-brachial index report

The FHS Executive Committee has appointed a Results Notification Sub-Committee to review forthcoming results protocols.

Examples of specific indices that are reported include blood pressure, ECG, Pulmonary Function Tests, Ankle-brachial index, Physical Activity, Bone Density*, and significant medical history or physical findings obtained by the clinical physician.

D. Laboratory Testing and Novel Biomarkers

The Framingham Heart Study laboratory notifies a participant’s physician in the event of a laboratory result outside the expected range, or as requested by the participant. These results are called and faxed. The FHS exam committee has a sub-committee on laboratory results reporting. At the beginning of each examination cycle, the sub-committee reviews the proposed analytes to be measured and determines which markers should be reported back to the participants. This scheme is based on clinical actionability. This sub-committee, along with the laboratory committee, also decides on alert values that would trigger an expedited notification.

Examples of laboratory testing results that are reported back to our participants include Cholesterol, HDL, Triglycerides, Glucose, Creatinine, HbA1c, Albumin, Calcium, Bilirubin, AST, ALT, WBC, RBC, Hemoglobin, Hematocrit, Platelet Count, and CRP levels. Examples of our alert values for expedited notification can be found in the Table below.

Test	Reference Range	Call Values	Gen3	Omni G2	Offspring
Albumin	3.5–5.2 g/L	<3.0 g/			
ALT	F:<34 / M:<41 U/L	>60 U/L	21	7	9
AST	F:<33 / M:<42 U/L	>60 U/L	5	2	4
Total bilirubin	<1.3 mg/100mL	>3.0 mg/100mL			
Calcium	8.4–10.2 mg/100mL	>11.0 mg/100mL	1		2
Cholesterol	<200 mg/100mL	>350 mg/100mL	2		
Fasting glucose	<126 mg/100mL	Fasting, non-diabetic >125 mg/mL Non-fasting, non-diabetic >200 mg/mL Diabetic >300 mg/100mL	7	1	15
2 hr glucose	<140 mg/100mL	≥ 200 mg/100mL	9	1	NA
HbA1c	4.8–5.9 %	Non-diabetic ≥ 6.5	7	4	16
Phosphorus	2.7–4.5 mg/100mL	<2.0 mg/100mL			
Triglycerides	<150 mg/100mL	>500 mg/100mL	2		1
Serum creatinine	F:0.5–0.9 / M:0.7–1.2 mg/100mL	>2.0 mg/100mL [except part. on dialysis]	1		4
WBC	4.5–11.5 (x 10 ³ /uL)	<2.0 or >20.0 (x 10 ³ /uL)	2	1	2
RBC	F: 3.7–5.2 / M: 4.4–5.7 (x 10 ⁶ /uL)	<3.0 or >6.0 (x 10 ⁶ /uL)	1	1	2
Hemoglobin	F: 10.5–15.0 / M: 12.6–17.0 g/100mL	<10.0 or >17.0	5		5
Hematocrit	F: 33–45 / M: 37–48 %	<30 or >60 %			4
Platelet count	175–400 (x 10 ³ /uL)	<70 or >500 (x 10 ³ /uL)	2		5

In addition to the analytes and laboratory that are generated in the setting of ongoing FHS exam cycles, FHS has a biorepository consisting of banked blood and urine samples. All applicants to the FHS laboratory committee are asked whether their produced analyte is actionable, and if so, to provide a plan for notification. This is then reviewed by the laboratory committee and the process as outlined above. Irrespective of actionability, we do not report results based on frozen samples that are more than 10 years old.

E. Imaging

Each imaging modality is evaluated on a case-by-case basis based on our overarching principles as laid out above.

For echocardiography, we send out results for major abnormalities: mild or greater degree of LV systolic dysfunction, aortic root dilation ≥ 5 cm, moderate to severe LVH, moderate or greater valve regurgitation or stenosis.

For carotid ultrasound assessment, we report carotid stenoses > 75 percent.

For brain MRI, all MRI scans are read by a board-certified radiologist within 2-3 days and a written report is sent to the FHS coordinator. Then, a board certified, licensed neurologist review the scans within 3-14 days and decide on the course of action, which can include: 1) If scan is within normal limits: Send a letter to the participant that the MRI showed nothing outside the normal range, with the caveat that this was a research and not a clinical MRI; 2) If scan is clearly abnormal and the abnormality is new/unexpected based on FHS records: Send the PCP the MRI report and give him/her a call to alert him. We also call the participant and send him/her a letter advising them to discuss the report with their PCP. If the participant does not have a PCP we ask them to obtain a PCP and send them the report; 3) For findings of doubtful clinical significance we follow the same protocol as above but the letter to the participant identifies the anomaly as one of doubtful clinical significance; 4) If the scan is clearly abnormal but the finding is known/expected (old stroke, old surgery etc.) we again follow the same protocol as #2 but the letter and phone call clarify that this is an expected abnormality.

Chest and Abdominal CT Scans: We have several different types of results reporting, including incidental findings (IFs), coronary calcium scores, and vertebral fractures. Our approach is as follows.

All CT scans are read by board-certified radiologists, who identify whether there is an IF. If the scan is a follow-up scan, the radiologist acknowledges whether the IF has progressed. Reports are then sent to the physician and the participant received a notification. Vertebral fractures were assessed off the scout films as part of an ancillary study. All Grade 2 and higher vertebral fractures were over-read by a board-certified bone radiologist and we are in the process of notifying our participants.

For coronary calcium, our current reporting scheme is based on the principle of balancing reasonable reporting with extreme values and at the same time the state of current scientific knowledge. Our current strategy is thus conservative and consistent. Based on these principles, our specific criteria are to report at cut-points that exceed the Hoff age-and-gender specific 90th percentile thresholds (see Appendix Table A at the end of the report), with the caveat that we do not report scores < 50 . This scheme is consistent with our CT pilot study, and our first MDCT scans, which were acquired in 2002-2005.

In 2010, our OSMB asked us to reconsider this reporting threshold: “The Board noted the continuing use of alert values for coronary artery calcification based on > 90 th percentile and recommended that the alert values be modified to reflect current practices.”

With our philosophy in mind, we proposed to maintain our current reporting guidelines for the following reasons: 1) there is no evidence to suggest that CAC reporting, in unselected asymptomatic community-based individuals, alters outcomes, 2) there is no clear consensus on what level to report, and 3) local clinical practice for use and interpretation of CT scanning is conservative. Given the above rationale, we did not deem a change in our reporting strategy this to be necessary. We have discussed this strategy with our external CT Advisory Committee (Dr. Alan Taylor and Dr. David Bluemke) and our Ethics Advisory Committee, who have agreed with this approach. Our Ethics Advisory Committee includes James Alderman MD, a local community cardiologist, who agreed and raised the question whether reporting these tests would provide any actionable results.

Moving forward into 2012, we anticipate that the state of the science will continue to evolve and thus we are committed to revisiting this and to modify our approach to report all scores (not just high scores) in the future. Any future studies conducted would be evaluated along with the OSMB on an ongoing basis to determine the level of actionability.

F. Genetics and Genomics

Now that the BUMC IRB has fully approved the amendment concerning reporting genetic results to a few participants who have a trait for hemochromatosis or Familial Mediterranean Fever, the FHS executive committee will make arrangements for implementation of the protocol for notification.

Appendix

Coronary Calcium Score – Reporting 90th Percentile

Age (years)	Men 90th Percentile	Women 90th Percentile
<40	14	3
40-44	59	4
45-49	154	22
50-54	332	55
55-59	554	121
60-64	994	193
65-69	1299	410
70-74	1774	631
>74	1982	709

6 Estonian Genome Project

Provisions from the project's consent form⁹⁵:

- “I have the right not to be aware of my genetic data, hereditary characteristic and genetic risks obtained as a results of genetic research
- I have the right to be aware of my genetic data and other data about me stored in the Gene Bank, except my genealogy. I have the right to genetic counselling upon accessing my data stored in the Gene Bank. I can access my data stored in the Gene Bank free of charge.”

⁹⁵ Information taken from <http://www.geenivaramu.ee/for-donors/gene-donor-consent-form.html> (accessed April 2013).

⁹⁶ Information taken from www.generationscotland.org/ (accessed June 2015).

⁹⁷ Information taken from <http://www.twinsuk.ac.uk/twin-zone/faq> (accessed June 2015).

7 Generation Scotland⁹⁶

“Will participants be told the results?”

After the clinic visit, Generation Scotland will give participants health information on some important clinical measurements such as weight and blood pressure. Participants can choose whether they would like their GP to receive a copy of the results.

Generation Scotland won't give participants any genetic information that arises from analysis of their DNA. That information wouldn't be passed on to insurers or employers either. Any information we get from participants or their health records would remain strictly confidential.

Will Generation Scotland carry out paternity testing?

Paternity testing is a sensitive issue. It is a scientific process that can positively identify relationships between people from their DNA. As part of the Scottish Family Health Study, researchers will perform tests to check that family members are genetically related, because this is essential for the success of the study. The researchers who carry out these tests will not know, or be able to find out, the identities of the people who gave the samples. Generation Scotland will not pass the results of family testing back to families. Requests from participants for paternity testing will not be considered.”

8 TwinsUK⁹⁷

“What are the benefits of participating?”

Apart from being immensely valuable to our research at the twin research unit, the visits are also beneficial to the twins. During the twin visit the twins have the opportunity to have a health check that a GP would not usually carry out. At a typical twin visit twins may have their fasting blood glucose and cholesterol checked, an ECG (electrical recording of the heart) a lung function test as well as a bone density scan. We may be able to pick up early osteoporosis, for example.”

9 Kaiser Permanente Research Program on Genes, Environment and Health (USA)⁹⁸

“Will the RPGEH return results to me?”

No. You will not receive personal health or medical results from taking part in the RPGEH. We do not expect that results from the RPGEH will be the kind of information that you or your health care providers would use to make decisions about your current health care. However, if scientists discover information as a result of RPGEH research that we believe is of substantial medical importance to you, we will re-contact you and ask if you want to learn the results.”

10 LifeGene (Sweden)

Extract from the LifeGene Ethics Policy (Version 3.2, February 2009)⁹⁹

“LifeGene will aim to ensure that participants understand that enrolment does not provide them with a general health check. LifeGene is primarily a research endeavor and not a health care screening program in the clinical setting. For instance, at the IPT, personnel are not primarily physicians and do not have access to full medical records. As a consequence, the significance of the observations might not be clear and LifeGene staff would not be in position to interpret their implications fully. Further, it is not likely to be constructive, and might even be harmful (including causing undue alarm and having potentially adverse effects on insurance and employment status), to provide information without prior counseling or support. For these reasons, LifeGene will only provide some carefully considered individual health information to participants. However, it is possible to provide participants with the results of some measurements or observations at several occasions: at the IPT visit (e.g. blood pressure or incidental findings), from the front end analysis (e.g. red cell count, cholesterol level), and later as results arise from research studies (e.g. genetic or biochemical information).

What kind of results and what measurements that will be provided to participants are not defined at present. This has to be processed by LifeGene in collaboration with relevant medical expertise, e.g. from the Swedish Society of Medicine, which can provide the clinical experience needed. Furthermore, LifeGene has to collaborate with those likely to manage the participants who have received information potentially relevant to their health, i.e. the health care system. Any proposed feedback must therefore be supported by the relevant health care institutions. In Sweden, most

health care institutions are on the regional and local levels. Thus, the support of SKL and other relevant institutions is of great importance.

The personnel providing the feedback must be trained professionals who are able to explain the implications for the individual regarding his or her health information. In the case of especially sensitive information with relevance for others, such as relatives, proper counseling is needed.

Specifically, provision of health information at the three stages will cover:

At the IPT visit: Participants will receive some of the measurements taken during the enrolment visit (e.g. blood pressure, lung function, height, weight, estimated amount of fat), if so consented. Consequently, a printed report will be provided at the end of their visit as a means of feeding back such measurements. The data will also be available at a personal web-site for the participants. By reporting standard ranges, the participant should be provided with sufficient information to give meaning to the measurements taken, so that they may act on the results if necessary and arrange to see their GP or other relevant health professional. The legal duty of care for staff will be determined by the research context, and will apply mainly to safe and competent collection of questionnaire data, measurements and blood or other samples. LifeGene will inform relevant health care institutions when the project is initiated about its existence and modus operandi. LifeGene staff should be able to recommend to participants where in the health care system they should turn in case of abnormal measurements or incidental findings.

Front end analysis: Prior to storage of samples, LifeGene is planning to conduct routinely only few analyses in biological material, including investigations that cannot be done subsequently on stored samples (such as hematology). LifeGene will feed back some of these analyzes to participants, if so consented. By reporting standard ranges, the participant should be provided with sufficient information to give meaning to the analyses taken, so that they may act on the results if necessary

98 Information taken from: www.dor.kaiser.org/external/DORExternal/rpgeh/faq.aspx?ekmense=194f64c3_47_69_btnlink#30 (accessed June 2015).

99 Information taken from: http://lifegene.ki.se/ethical_issues/index_en.html (accessed June 2015).

100 Information taken from: www.lifegene.se/In-english/Participation/ (accessed June 2015).

101 Information taken from: www.lifegene.se/In-english/Participation/ (accessed June 2015).

102 Information taken from: www.lifegene.se/In-english/Privacy (accessed June 2015).

and arrange to see their GP or other relevant health professional. Then, if needed, participants must receive proper and professional support and counseling regarding the implications of the findings either from LifeGene or LifeGene has to ensure this is received from a relevant health institution.

Later, as a result of research studies: In normal healthcare settings, tests are conducted at the individual level immediately after sample collection; they search for specific conditions or outcomes; and, in the case of genetic tests, pre- and post-test counseling is provided. In LifeGene, given the lack of knowledge at recruitment about the tests that might be done in this research context (and, hence, the inability to provide specific counseling beforehand), we will not in general provide participants with information (genetic or otherwise) about their own individual results derived from examination of the database or samples by research undertaken after enrolment (with the exception specified below). Instead, the overall findings and implications of results that derive from LifeGene will be made available to participants and the wider community so that they can influence public health strategies (including, where appropriate, the introduction of screening for newly discovered risk factors).

However, there may be findings of new biomarkers implicating a very high risk of a preventable and serious disease. If such findings are made and corroborated, LifeGene may contact individual participants to communicate these findings, if LifeGene in agreement with relevant medical expertise finds this defensible. This will only be done provided the participant has agreed to be contacted with such information, since this would require de-anonymization of the participant. Such re-contact is made through inviting the participant to an individual counseling session with a professional counselor. The case handling will be performed in collaboration with relevant health care institutions. LifeGene commits itself not to contact genetic relatives to communicate this kind of information.”

Information from the LifeGene website

“Physical test

At the LifeGene test centre, we measure your height and weight, fat distribution in the body, blood pressure, lung function and perform a hearing test. You will get the results immediately after the measurements are completed.”¹⁰⁰

“Sampling

We will ask you to provide blood and urine samples. Samples taken from adults total up to 60 ml of blood

(a normal blood donation measures about 400 ml). For children, the amount depends on age. A topical anesthesia is available to make leaving blood samples more comfortable for children. Results from the blood sample analysis, are available within a week on your personal web page.”¹⁰¹

“You are entitled to know what information is stored about you

An important part of privacy protection in the context of research is that all participants have a right to know what information is held about them. You are therefore entitled to find out what information exists about you free of charge once per year. If the information is incorrect, incomplete or irrelevant, you also have the right to request that it be corrected or deleted.”¹⁰²

“You will receive the following results

Measurement of fat mass: A bioimpedance scale, measures your weight, body composition (amount of fat and fat-free mass) and BMI. A slight, yet noticeable, electrical current is sent through the body and based on the electrical resistance, body composition is calculated. Body fat is a good indicator of overall health and the measurement gives a better picture of the body than a normal weight measurement. Bioimpedance is done on participants from 7 years old and up.

Measurement of heart rate and blood pressure: High blood pressure increases the risk of heart disease and kidney damage and is highly influenced by lifestyle factors such as diet and exercise. Heart rate and blood pressure are measured manually. Heart rate and blood pressure are measured for participants from 5 years old and up.

Cholesterol: There is a clear link between the food you eat and your cholesterol. Measuring blood cholesterol levels gives an indication of the risk of developing cardiovascular disease.

Waist / hip ratio: Today’s research agrees that waist/hip ratio is a better measure of the risk of developing cardiovascular disease than BMI, especially for those with “normal” body weight. Waist/hip ratio indicates how much of the body’s fat stores are located on the abdomen and is measured using an old fashioned tape measure. Done on participants from 6 years old and up.

Lung function: A pulmonary function test is done by using spirometry to examine how the lungs work. It is measured by blowing into a mouthpiece that is connected to a device called a spirometer. It measures the speed and volume of air that is blown out. Conducted from 10 years old and up.

Hearing test: Our hearing test gives you an indication of how well you hear. The hearing test is done from 6 years old and up.

When will I receive the results?

You get results as soon as the measurements and tests are completed. Results from the blood sample analyses will be available within a week. The result of the test performed at the test center will be available directly after the visit.

You can see all of your results when you log in at www.lifegene.se.

What if one of my results requires medical follow-up?

If the results show that a medical follow up is needed, you will be advised to consult your family doctor.”¹⁰³

11 NuGene¹⁰⁴ (USA)

“Will I find out the results of the research?”

Neither you nor your doctor will receive the results of any research done on your DNA. However, all participants have the option to receive a newsletter containing updates on all current research and findings, as well as information regarding future research from the NUgene Project.”

12 String of Pearls¹⁰⁵ (Netherlands)

Extracts from the String of Pearls Framework Regulation (Version 11.5 18 June 2009)

Definitions:

Serendipity Findings: Unforeseen results from Research which are not related to the protocol on which the Research is based and which have or may have direct significance for the health of a single Donor or a particular group of

Pearl: A joint venture focusing on a specific medical condition. A Pearl consists of a Pearl Coordinator and several Pearl Participants who, in the context of the String of Pearls and under the conditions set out in this Regulation and on behalf of the Parties involved, collect and Provide Human Tissue and Donor Data for Research and who are furthermore responsible on behalf of Parties for ensuring that the tasks of a Pearl are carried out as defined in this Regulation.

Party(ies): One or more parties connected with this Regulation.

Information on research outcomes:

...

3) The Party on behalf of which the Donor Data and the Donor Material are Provided shall be informed by the Central Organisation about Serendipity Findings

that have been notified to the Central Organisation. Each Party shall ensure that Serendipity Findings are reported in the correct manner in accordance with its own internal policy.

4) The agreements with the external Researcher shall specify that Findings as referred to in paragraphs 2 and 3 above obtained from Research by the external Researcher concerned shall be reported to the Pearl.

5) Donors shall under no circumstances be informed directly by the Researcher or the Pearl carrying out the Research unless the Researcher is also the Treating Physician.

13 Western Australia DNA Banks¹⁰⁶

This is a central resource for different collections for which different feedback policies might apply.

Can I access my own DNA if it is stored in the WA DNA Bank?

No. Your DNA has been collected strictly for medical research purposes only and the WA DNA Bank cannot release it back to you personally for any reason. To better understand the ethical guidelines under which medical research is conducted you may wish to access detailed information from the National Health and Medical Research Council.

Will the WA DNA Bank provide the donors with any information or results that arise from research carried out on their DNA?

The WA DNA Bank itself does not provide any information or results that have arisen from research carried out on the DNA stored within the facility. If you are participating in a research study you would have been given detailed guidelines about the study when you consented to participate, including how information arising from the research was to be conveyed back to the participants. If you are unclear about any aspect of the study you were (or are) involved in you are strongly encouraged to contact the study coordinator directly to answer your queries or to discuss any concerns you may have.

103 Information taken from: www.lifegene.se/In-english/QA/ (accessed June 2015).

104 Information taken from: <https://www.nugene.org/participate/faq/> (accessed April 2013).

105 Information taken from: www.string-of-pearls.org/uploaded/FILES/htmlcontent/Framework%20Regulation%2011.5.pdf (accessed April 2013).

106 Information taken from: www.genepi.meddent.uwa.edu.au/enabling-resources/biobanking/frequently-asked-questions (accessed June 2015).

14 International Cancer Genome Consortium

The International Cancer Genome Consortium (ICGC) has been organized to launch and coordinate a large number of research projects that have the common aim of elucidating comprehensively the genomic changes present in many forms of cancers that contribute to the burden of disease in people throughout the world.

Consortium guidelines refer to recommendations made by ICGC working groups that offer advice as to what is believed to constitute “best practices” at a given time.

“ICGC guidelines for information that should be provided to participants regarding prospective research (ICGC acknowledges that the informed consent process used by ICGC members will necessarily differ according to local, socio-cultural and legal requirements):

Provided it is agreed at recruitment, if clinically important and validated findings emerge during the initial recruitment and screening phase, or in the early research, attempts will be made to pass this information back via the clinician, by whatever mechanism may be agreed at the local level.”¹⁰⁷

15 West of Scotland Twenty-07 Study¹⁰⁸

Information sheet, Wave 5, version 4, 3rd September 2007

“What will be involved?”

You will be contacted by a nurse to arrange a convenient time for them to visit you. Once an interview time has been arranged the nurse will send you two booklets to complete before the interview. This should take no more than 15 minutes.

The interview includes three main parts.

First, the nurse will ask you questions about your health, and your living and working circumstances now and over the last few years. The information will be recorded on a laptop computer and we expect this will take about an hour to an hour and a half, although it will vary according to your particular circumstances.

Secondly, the nurse would also like to complete some physical measures with you. These will be your pulse, blood pressure, height, weight, waist and hip circumference, lung function, reaction time (to assess the speed of your reactions) and the AH4 a test of your reasoning skills. In addition there will be three new measures this time, which we hope you will agree to do: your sitting height; your internal body fat by directing

a very mild electric impulse through electrodes attached to your hand and foot, which is entirely safe and will not hurt at all (bioimpedance); and your hand grip strength, which gives an indication of your upper body strength. We expect the physical measures to take about three-quarters of an hour to complete.

Finally, if you agree, in this final phase of the Study we would also like to take blood samples which will give us biological markers of your health. We would like to take 39ml of blood, which is about 7.5 teaspoons. You can take part in the study without giving a blood sample if you wish. We will tell you a little more about this below.

Before the nurse begins the interview, she will ask you to sign a consent form agreeing to take part in the study. During the interview, you can choose not to answer any questions, refuse any physical measure you do not want taken or stop the study at any time. We will also ask you to sign a consent form before we take the blood samples and again you can refuse any measure at any time. If you choose to do the physical measures and give a blood sample, after we have analysed your data, we will send your results back to you and your GP, if you wish.

Why are we asking for a blood sample and what will happen to it?

The blood sample is required to give us more detailed information about the general health of the people taking part in the West of Scotland Twenty-07 Study. However, before you agree to donate a blood sample, it is important that you understand what will happen to it now and how it may be used in research in future.

- First, a portion of the sample will be used right away for general health screening. This will involve testing the sample for levels of lipids or fats (e.g. cholesterol) in the blood and other common markers of health (e.g. blood cell count, liver and kidney function, markers for future heart problems, diabetes, and blood cell ageing). It will not involve testing for blood borne viruses, HIV or Hepatitis B or C. We realise that the results of the health screening may be of importance to you and, at your request, we will send you a copy of selected results and, with your permission, a copy to your GP together with the results of some of the physical tests. This is covered specifically in the consent form that you will be asked to sign.

¹⁰⁷ Information taken from: www.icgc.org/icgc/goals-structure-policies-guidelines/e1-informed-consent-access-and-ethical-oversight (accessed June 2015).

¹⁰⁸ Information taken from: <http://2007study.sphsu.mrc.ac.uk/information-for-participants.html> (accessed June 2015).

- Second, we wish to carry out a genetic analysis because research has shown that our genetic make up may influence our risk of developing certain illnesses. To do this we will extract some DNA (the substance that makes up your genes) from a portion of your blood sample. The DNA sample will be assigned a unique code so that your identity will be protected at all times then stored by the MRC for use in future research into the genetic basis for disease and the response to treatment. It will then be transferred to the MRC Twenty-07 Study Tissue Bank where it will be available for use in future research. A separate Information Sheet (2) and Consent Form (3) to cover this has been provided. Such research will take place in the future and hence we cannot give you any genetic information now. We will not give you genetic information in the future because we cannot say now what bearing it might have on your health.
- Third, the remaining portion of the blood we collect will be transferred to the MRC Twenty-07 Study Tissue Bank where it will be available for use in future research. A separate Information Sheet (2) and Consent Form (3) to cover this has been provided.”

16 Qatar Biobank¹⁰⁹

Will any of my assessment results be given back to me?

If you want them, you will be given some of the test measurements and results, including, height, weight, percentage body fat, blood pressure and lung function, plus how they compare with the accepted norms for your particular circumstances. A doctor will check your results and you will be advised if any results are not in the normal range, and a medical referral process will be available.

If you say from the start that you do not want to know any of your results, we will respect this and withhold them.

109 Information taken from: <http://www.qatarbiobank.org.qa/find-out-more/faq> (accessed June 2015).

110 Information taken from: <http://www.genomicsengland.co.uk/the-100000-genomes-project/faqs/ethics-and-consent-faqs/> (accessed May 2015).

17 Genomics England/100,000 Genomes Project¹¹⁰

Type of finding*	Pertinent finding (also known as a primary finding).
Description	A pertinent (primary) finding is relevant to the explanation, main diagnosis or treatment of the disease for which the patient was referred into the 100,000 Genomes Project by their clinician (i.e. the patient’s cancer, rare disease or response to infection).
Nature of the information to be fed back	To be reported as a pertinent (primary) finding, mutations must be ‘Known to be Pathogenic’ (KP) i.e. sequence variation is previously reported and is a recognised cause of the disorder. Mutations that are ‘Expected to be Pathogenic’ (EP) will be referred to the appropriate GeCIP domain for confirmation. NHS clinicians will be integral to confirmation of pathogenicity through GeCIP. This will not be fed back to patients unless an EP mutation becomes a KP. i.e. sequence variation is previously <i>unreported</i> and is of the type which is <i>expected</i> to cause the disorder.
How feedback will happen	Pertinent (primary) findings will be given to the referring clinician or clinical team by the 100,000 Genomes Project for discussion with the patient after the NHS has validated these findings. It will be emphasised to participants that findings of ‘Known Pathogenicity’ do not (usually) equal 100% penetrance.
Approach to consent or refusal	A participant’s consent to receive pertinent findings will be integral to their participation in the 100,000 Genomes Project. If such consent is refused, participation will not be permitted.

Type of finding*	Secondary finding (additional looked-for findings of healthcare importance).
Description	A secondary finding is an additional, looked-for health related finding, that is not pertinent to (or a primary cause of) the main condition. It may be found <i>in addition to</i> (or <i>in the absence of</i>) any pertinent finding.
Nature of the information to be fed back	Genomics England will also look for genomic findings that are known to cause serious conditions for which there is good evidence that knowing about them could influence healthcare. We will start with a limited list of relatively rare conditions, but will adapt this list as more evidence accumulates: <ul style="list-style-type: none"> • Hereditary non-polyposis colorectal cancer (HNPCC)/ Lynch syndrome (genes: mismatch repair genes MLH1, MSH2, MSH6, PMS2) – adult onset** • Familial adenomatous polyposis (FAP) (gene: APC) • MYH-associated polyposis (MAP) (gene: MutYH) • Hereditary, breast and ovarian cancer (genes: BRCA1 and BRCA2) – adult onset • Von Hippel-Lindau syndrome (gene: VHL) – child and adult onset • Multiple endocrine neoplasia type 1 (gene: MEN1) – child and adult onset • Multiple endocrine neoplasia type 2 (gene: RET) – child and adult onset • Familial medullary thyroid cancer (FMTC) (genes: RET and NTRK1) – child and adult onset • Retinoblastoma (gene: RB1) – child onset • Familial hypercholesterolaemia gene: LDLR- child onset- and also APOB and PCSK9 – child and adult onset*** <p>Please note: the Genomics England approach to findings relating to adult onset conditions in children will be in accordance with the BSGM policy on genetic testing of children** i.e. only the mutations in genes that are known to cause childhood-onset disease will be looked for in the case of minor participants.</p>
How feedback will happen	Participants will be asked whether they would like these secondary findings to be actively sought. If they consent to this, information relating to secondary findings will be looked for and given to the referring clinician or clinical team for discussion with the participant. (Without this consent these secondary findings will not be actively sought.) Following positive or negative confirmation regarding these secondary findings, a health professional will feed back to the participant on these results. Some variants in this gene list may not yet have sufficient evidence for their clinical impact to be known, or clearly predicted. These variants of uncertain significance will not be reported. An important aim of the 100,000 Genomes Project is to generate evidence about the clinical relevance of new findings. Our understanding of the clinical significance of a secondary finding will change over time as more evidence is gathered.
Approach to consent or refusal	Consent for the feedback of these secondary findings will be by opt-in to feedback. Patients who do not wish to receive information about these findings are free to refuse to consent. Participants can opt-in to consent to the list(s) of identified conditions to be looked-for at the time of consent, plus if they wish, to findings made as that list extends. This will permit results regarding other conditions that meet this criteria in future to be looked-for and fed back.

Type of finding*	Carrier status. Under certain circumstances carrier status may affect future children.
Description	Autosomal recessive. Where both parents participate, we will be able to identify a limited list of double carrier states where knowledge might affect future family planning. X-linked disorders in women carriers.
Nature of the information to be fed back	Sickle cell anaemia Cystic fibrosis Beta thalassemia Congenital adrenal hyperplasia 21-hydroxylase deficiency Alpha thalassemia Spinal muscular atrophy type I Duchenne muscular dystrophy Adrenoleukodystrophy Haemophilia A (inversion)
How feedback will happen	Participants will be asked whether they would like these carrier states to be actively sought. If they consent to this, information relating to carrier states will be looked for and given to the referring clinician or clinical team for discussion with the participant. (Without this consent these carrier status will not be actively sought.) When either positive or negative results are confirmed regarding these looked-for findings, a health professional will feed back to the participants.
Approach to consent or refusal	A list of conditions for opt-in looked-for carrier status. For double carrier of recessive feedback will be undertaken for those who opt-in, provided both parties in the couple consent to seeking and return of these results as a couple . Or a woman carrying an X-linked disorder consents to opt-in to feedback.

Type of finding*	Incidental findings. A sub-category of additional findings that are not actively sought. Also described as 'unsolicited' findings****
Description	This is any secondary health-related finding that has not been included in the gene list above.
Nature of the information to be fed back	In the clinical phase of the 100,000 Genomes Project, such findings will usually not come out of the analysis, but just occasionally it is possible that in diagnosing the Primary finding, an Incidental finding is noted that does not belong to the gene lists above. These examples are expected to be very rare, but will need discussion and evaluation within GeCIP in order to decide whether the evidence is certain enough in regards to clinical relevance that disclosure to the clinician is appropriate. In most cases incidental findings in this group will be found in the research stages of Genomics England and will only be utilised in the clinical setting once they are assigned to the list of secondary findings above.
How feedback will happen	<i>Incidental</i> findings will usually not be sent to clinicians or patients by Genomics England.
Approach to consent or refusal	The policy on not feeding back incidental findings will be explained to the patient at the time of consent.

18 UK Biobank

*Extract from the UK Biobank Ethics and Governance Framework Version 3.0 (October 2007)*¹¹¹

Provision of health information to participants

UK Biobank will aim to ensure that participants understand that enrolment does not provide them with a health check. In principle, it would be possible to provide participants with the results of some measurements or observations at any of three stages: at the initial assessment visit (e.g. blood pressure or incidental findings), in the initial stage before samples are stored (e.g. white cell count), and much later as results arise from research studies (e.g. genetic or biochemical studies).

However, the value of such feedback is questionable because the data would be communicated outside of a clinical setting and would not have been evaluated in the context of the full medical record. As a consequence, the significance of the observations might not be clear and UK Biobank staff would not be in position to interpret their implications fully. Further, it is not likely to be constructive, and might even be harmful (including causing undue alarm and having potentially adverse effects on insurance and employment status), to provide information without prior counselling or support (which UK Biobank will not be able to provide: as explained below). For these reasons, UK Biobank will generally not provide health information to participants, and a clear explanation of this policy (and the few exceptions) will be provided in the participant information material.

Specifically, provision of health information at the three stages will be covered:

At the initial assessment visit: It would be impractical and inappropriate to conceal from participants some of the measurements taken in their enrolment visit (i.e. blood pressure, height, weight, estimated amount of fat). Consequently, a printed report will be provided at the end of their visit as a means of feeding back such measurements. By reporting standard ranges, the participant should be provided with sufficient information to give meaning to the measurements taken, so that they may act on the results if necessary and arrange to see their general practitioner or other relevant health professional.

The legal duty of care for staff conducting enrolment will be determined by the research context, and will apply mainly to safe and competent collection of questionnaire data, baseline measurements, and blood or other samples. They will not have the same duty of care that they would have in a clinical setting. However, even in this research context, there may be occasions when staff consider there to be a professional or ethical obligation to draw attention to abnormal measurements (such as elevated blood pressure) or incidental findings (such as possible melanoma). In such circumstances, participants will be encouraged to contact a relevant health professional.

Before samples are stored: Prior to storage of samples, UK Biobank is planning to conduct routinely only those few investigations that cannot be done subsequently on stored samples (i.e. haematology). As is the case with other measurements that may be conducted on stored samples (see below), these baseline measurements are being conducted outside of a clinical setting without prior counselling and support. Moreover, all such analyses will be conducted on anonymised samples without other relevant medical information about the individual. Consequently, these individual results with personal identifying details will not be provided to a participant or to anyone else. A clear explanation of this policy will be included in the participant information material.

Later, as a result of research studies: In normal healthcare settings, tests are conducted at the individual level immediately after sample collection; they search for specific conditions or outcomes; and, in the case of genetic tests, pre- and post-test counselling is provided. But, given the lack of knowledge at recruitment about the tests that might be done in this research context (and, hence, the inability to provide specific counselling beforehand), UK Biobank will not provide participants with information (genetic or otherwise) about their own individual results derived from examination of the database or samples by research undertaken after enrolment. Instead, the overall findings and implications of results that derive from UK Biobank will be made available to participants and the wider community so that they can influence public health strategies (including, where appropriate, the introduction of screening for newly discovered risk factors).

¹¹¹ Information taken from: <http://www.ukbiobank.ac.uk/wp-content/uploads/2011/05/EGF20082.pdf> (accessed June 2015).

UK Biobank Ethics and Governance Council

Wellcome Trust, Gibbs Building
215 Euston Road, London NW1 2BE

T +44 (0)20 7611 8335

F +44 (0)20 7611 8545

E EGCinfo@wellcome.ac.uk

W www.egcukbiobank.org.uk