

# Managing incidental and pertinent findings from WGS in the 100,000 Genomes Project

A discussion paper from  
the PHG Foundation

April 2013

**Authors: Alison Hall, Nina Hallowell and Ron Zimmern**

This paper can be downloaded from our website:  
[www.phgfoundation.org](http://www.phgfoundation.org)

**Published by PHG Foundation**

2 Worts Causeway  
Cambridge  
CB1 8RN  
UK

Tel: +44 (0) 1223 740200

Fax: +44 (0) 1223 740892

© 2013 PHG Foundation

Correspondence to:  
[alison.hall@phgfoundation.org](mailto:alison.hall@phgfoundation.org)

*How to reference this paper*

**Managing incidental and pertinent findings  
from WGS in the 100,000 Genomes Project,  
PHG Foundation (2013),  
ISBN 978-1-907198-12-0**

The PHG Foundation is the working name of the Foundation for Genomics and Population Health, an independent charitable organisation (registered in England and Wales, charity No. 1118664 company No. 5823194), which works with partners to achieve better health through the responsible and evidence-based application of biomedical science

## Contents

1.	Background	<b>2</b>
2.	A typology of information generated by WGS	<b>2</b>
3.	Research versus clinical care	<b>6</b>
4.	The disclosure of findings generated by WGS undertaken in a clinical context	<b>8</b>
5.	The disclosure of findings generated by WGS undertaken in a research context	<b>10</b>
6.	Does the nature or application of WGS technologies change or influence these obligations?	<b>14</b>
7.	Consent and the 100K Genomes Project	<b>15</b>
8.	Recommendations	<b>17</b>

## 1. Background

1.1 The UK Government recently announced that the NHS will procure high throughput sequencing capacity and capability to deliver the sequencing of 100,000 genomes of NHS patients. The 100,000 Genomes Project (hereafter 100kGP) will in the first instance concentrate on sequencing patients with:

- (a) Rare diseases
- (b) Cancers
- (c) Infectious diseases.

The ethical underpinning of this proposal and the issues arising will be critically dependent on whether its primary purpose is clinical care or research or some mixture of the two. In order to discuss these ethical issues, we need to be clear about the status of the information that is generated in these different contexts by various methods of sequence analysis and interpretation (*e.g.* targeted arrays versus exome/whole genome sequencing).

1.2 The goal of this paper is to describe:

- (a) The different types of information generated by WGS
- (b) To detail how they arise in research and clinical contexts and
- (c) To suggest what ethical issues the disclosure of this information generates and how they might be addressed.

The paper will briefly look at what form of consent might be appropriate in the 100kGP before DNA/tissue samples are taken, and the extent to which there is an additional role for consent when disclosing WGS information to patients or research participants.

## 2. A typology of information generated by WGS

2.1 In order to discuss the ethical issues that may arise from the implementation of WGS in clinical and research settings we need to first outline and define the status of the findings that may emerge.

2.2 Findings obtained from WGS may be either scientifically significant, or not. By 'scientifically significant' we mean that there is robust statistical evidence of a relationship between the genomic characteristic (usually a genetic variant) and a particular phenotype. If there is insufficient evidence to support a genotype-phenotype relationship then the finding is often referred to as a variant of uncertain significance (VUS). Labelling a particular variant as a VUS does not mean that the variant is not associated with a particular phenotype, but rather that no significant statistical relationship has been established between the variant and the phenotype.

2.3 Over the past few years the terms **pertinent findings** and **incidental findings**<sup>1</sup> have been developed and used in the literature to refer to findings generated by WGS. The use of these terms indicates that commentators have become preoccupied with the (intentional or accidental) generation of findings rather than their subsequent use. In this paper we use the following definitions:

- **Pertinent findings** are findings that have been generated or sought with the purpose of answering a particular clinical or research question either by genotyping specific areas of the genome or by specifically interrogating those areas if the whole genome has been sequenced. For example, if a patient or research participant presents with a personal and/or family history of a particular cancer, then the test will seek to establish whether the genetic sequence includes variations that have been associated with susceptibility to that cancer.
- **Incidental findings** are additional findings concerning a patient or research participant that may, or may not, have potential health implications and clinical significance, that are discovered during the course of a clinical or research investigation, but are beyond the aims of the original test or investigation. For example, in a research study if exome sequencing is undertaken on parents and their child (as a trio) to establish the pathogenicity of a genetic variant and non-paternity is subsequently discovered, the finding of non-paternity would be regarded as an incidental finding as the test did not set out to determine paternity *per se*.

2.4 While we acknowledge the distinction between these types of findings, we believe that the most important ethical question concerning WGS findings is not whether they belong to one or other of these categories, but what we should do with them and the normative framework that we apply to such a decision.

2.5 This paper will focus on the disclosure of **scientifically significant** WGS findings that emerge during research or clinical investigations that are reasonably likely to have an impact on the physical or psychological health of an individual. In particular, we will look at the obligations to disclose or not, or act or not to act upon these findings. We note that the obligations to disclose will vary dependent upon the nature of the findings as described in 2.3 above. Figure 1 (page 3) sets out a taxonomy of WGS findings and some associated disclosure options.

2.6 A number of additional factors may need to be considered when assessing whether a finding should be disclosed. For clinically significant findings that have potential health implications, these include: the timing of the impact upon health, when this will come about, now or in the future; its scope, who it affects, the individual, their offspring or other

---

1 In the context of WGS the terms incidental findings, unsolicited findings, co-incidental findings and variants of unknown significance (VUS) have all been used without clear definition or any form of consensus (Wolf SM, Lawrenz FP, Nelson CA et al. Managing incidental findings in human subject research: analysis and recommendations. *J Law Med Ethics* 2008;**36**:219-248). There is also a lack of consistency in how they are used in the literature (Christenhusz GM, Devriendt K, Dierickx K (2012) To tell or not to tell? A systematic review of ethical reflections on incidental findings arising in genetics contexts. *EJHG*,**21**:248-255 doi:[10.1038/ejhg.2012.130](https://doi.org/10.1038/ejhg.2012.130)). This creates conceptual and analytical difficulties which are now being reiterated in policy making.

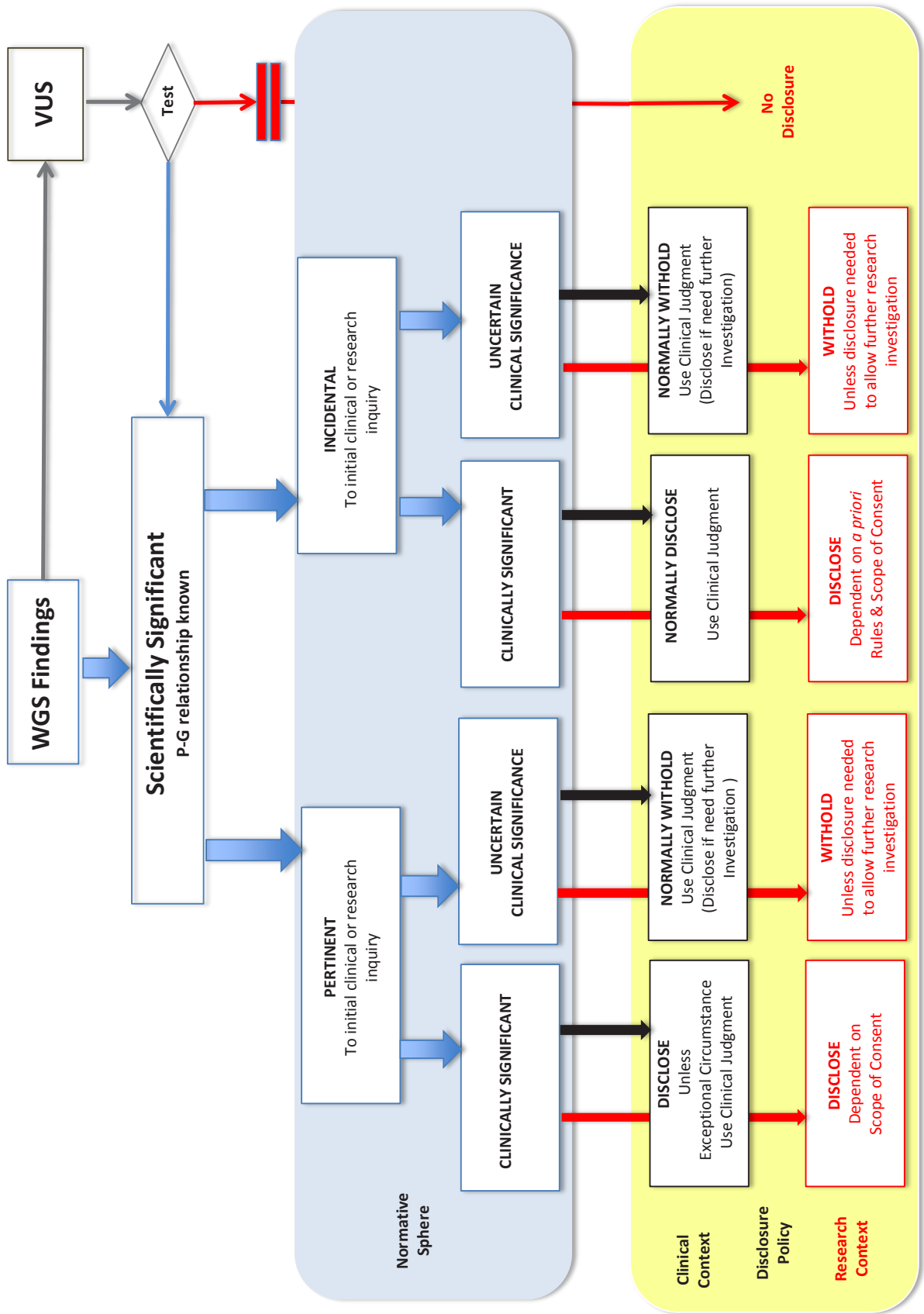


Figure 1

family members; its scale, whether its impact upon health is significant or trivial; and the probability of impact, whether the variant is completely penetrant or only marginally so. It may not always be clear, at least initially, whether or not disclosure is justified. Some scientifically significant findings will be variants of uncertain or marginal clinical significance (VUCS), particularly if WGS or exome sequencing is used; uncertain findings may require further clinical investigation<sup>2</sup>. It may only be after further tests that one can determine how to proceed with disclosure. The requirement for further investigation might necessitate disclosure of these findings even though their clinical significance is uncertain at the time of disclosure.

- 2.7 Routine clinical examination and investigation may involve testing for other disorders as part of the process of making a differential diagnosis and providing comprehensive care. If, however, some other investigation or test is explicitly conducted to generate information that is not related to the presenting complaint, we should regard that intervention as an example of opportunistic screening<sup>3</sup>. We are not concerned with opportunistic screening in this paper, but believe that both patients and research participants should be informed of the intention to undertake opportunistic screening if it is carried out, and should be required to give explicit and separate consent. Some commentators have argued that certain specific findings unrelated to the reasons for carrying out the WGS (whether in a clinical<sup>4</sup> or research context) should be explicitly investigated and disclosed to the patient or research participant. Our view is that this constitutes opportunistic screening and that failure to obtain specific, free and informed consent for so doing would be unethical even if failure to disclose such information could be detrimental to the health of the patient or research participant.
- 2.8 The question of what should be done with findings from WGS and what should be disclosed to patients or research participants has generated much debate. When formulating a disclosure policy there is a need to take into account whether the findings arise during a research intervention or a clinical investigation.

- 
- 2 For indications of frequencies of clinically relevant findings, see for example Johnston J et al (2012) Secondary Variants in individuals Undergoing Exome Sequencing: Screening of 572 Individuals Identifies High-Penetrance Mutations in Cancer-Susceptibility Genes. *Am J Hum Genet* **91**:97-108.
- 3 If genetic testing is carried out to determine a cancer patient's *BRCA1* or *BRCA2* mutation status and at the same time it is decided to undertake screening for mutations for familial hypercholesterolemia, the latter would be an example of opportunistic screening. The principles of clinical epidemiology suggest that the positive predictive value of a test, the probability of whether a finding is true or false, is related to the prevalence (the prior probability) of the disease in the population tested. For this reason, positive results emerging from screening tests rather than diagnostic tests are much less likely to be true positives and more likely to be false positives, due to the fact that the prior probability of the disease in question within the clinical population being investigated is likely to be higher than in a general population. Hence a finding identified incidentally during WGS is more likely to be a false positive finding than a true positive finding. For discussion, see Burke W, Tarini B, Press NA, Evans JP (2011) Genetic Screening. *Epidemiol Rev* **33**:148-164.
- 4 Green RC et al (2013) ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing. These recommendations propose that the use of clinical exome and genome sequencing should be contingent upon the patient accepting opportunistic screening and disclosure of a range of serious, clinically actionable diseases.

### 3. Research versus clinical care

- 3.1 The primary aim of the 100kGP is clinical, albeit with an understanding that the results of sequencing may be used for research purposes at a later date.
- 3.2 Research and clinical care are frequently understood as separate activities, deriving from very different motivations. Interventions carried out as clinical care are personalised; they are motivated by individual patients' needs and any risks are justified by anticipated benefits for the patient. Research interventions, on the other hand, are usually independent of patients' interests; they are hypothesis- rather than needs-driven.
- 3.3 In order to determine whether a particular activity is research or clinical care it can be helpful to question whether the rationale for the intervention is to benefit the individual patient, or the wider patient population. Other relevant questions include:
- Is the purpose just to enable the diagnosis in the patient?
  - Is the intention that diagnostic results or other patient data may be used for other purposes including research?
  - Is there an intention to screen opportunistically for other conditions not related to the diagnosis and what will be done with this information?
  - Is it intended that the patient's data be stored for future research use, and if so, in what form?
  - Will the patient's data be shared, with whom and for what purpose?
- 3.4 Distinguishing research from clinical activities is critical from an ethical standpoint. In both cases the ethical framework is driven by the principles of **beneficence, non-maleficence, justice** and **respect for autonomy**<sup>5</sup>. Within a clinical setting the obligations and responsibilities of the health professional place the welfare and the best interests of the patient at the heart of the clinical encounter and provide the starting point for ethical considerations. In the research setting consent and the protection of the research participant predominate.
- 3.5 The boundary between clinical and research activities is becoming increasingly blurred, particularly in the subspecialty of clinical genetics<sup>6</sup> and is growing with the use of genomic technology<sup>7</sup>. This arises because in a resource scarce environment, some genetic tests (*e.g.*

---

5 Beauchamp T & Childress J (2013) *Principles of Biomedical Ethics*. Fifth Edition Oxford University Press.

6 Hallowell N, Cooke S, Crawford G, Lucassen A, Parker M, Snowdon C (2010) An investigation of cancer genetics patients' motivations for their participation in research *J Med Ethics* **36**:37-45; Hallowell N, Cooke S, Crawford G, Parker M, Lucassen A (2009) Health care professionals' and researchers' understanding of cancer genetics activities: a qualitative interview study *J Med Ethics* **35**:113-119; Hallowell N, Cooke S, Crawford G, Parker M, Lucassen A (2009) Distinguishing research from clinical care in cancer genetics: theoretical justifications and practical strategies. *Soc Sci Med* **68**:2010-2017.

7 Ponder M, Statham H, Hallowell N, Moon J, Richards M, Raymond FL (2008) Genetic research on rare familial disorder



for rare diseases) can only be accessed through research protocols because there are no relevant genetic tests validated for clinical use within the NHS<sup>8</sup>.

- 3.6 The result of this increasing ambiguity is that research participants find it difficult to distinguish between research and clinical activities or outcomes, particularly when the researcher is also their clinician<sup>9</sup>. This confusion may lead to research participants subscribing to the 'therapeutic misconception'<sup>10</sup>. The therapeutic misconception frequently arises because research participants may perceive themselves receiving more "care" in a research than a clinical context<sup>11</sup>.
- 3.7 In the research setting, professional obligations do not (by and large) exist *a priori* unless the researcher is coincidentally also a physician or some other health professional bound by professional standards, such as the GMC guidelines in the UK<sup>12</sup>. The researcher's obligations are instead guided by the *International Declarations of Helsinki and Nuremburg* and the *Belmont Report*<sup>13</sup>, the intention of which are to prevent harm to research participants and ensure they are able to participate freely. Informed consent, therefore, plays a greater role in research; see, for example, the randomised controlled trial<sup>14</sup>. However, the fact that GMC guidelines address the duties of physicians undertaking research on research participants with whom they may not have a clinical relationship is evidence of the blurring of the boundaries between clinical and research activities, and raises questions about the limits

---

ders: consent and the blurred boundaries between clinical service and research *J Med Ethics* 34:690-4.

- 8 Indeed some commentators have suggested that where technologies such as WGS can only reasonably practically be accessed via research, then this may give rise to an obligation for genomic researchers to actively seek incidental findings in the future. Gliwa C, Berkman BE (2013) Do Researchers Have an Obligation to Actively Look for Genetic Incidental Findings? *Am J Bioeth* 13:2, 32-42.
- 9 Cooke S, Crawford G, Parker M, Lucassen A, Hallowell N (2008) Recall of participation in cancer genetics research projects. *Clin Ethics* 3:180-4.
- 10 Appelbaum PS, Roth LH, (1982) The therapeutic misconception: informed consent in psychiatric research. *Int J of Law and Psychiatry* 5:319-329; Appelbaum PS, Roth LH, Lidz CW, Benson P, Winslade W (1987) False hopes and best data: consent to research and the therapeutic misconception. *Hastings Center Report* 17: 20-24; Henderson GE, Churchill LR, Davis AM, Easter MM, Grady C, Joffe S, Kass N, King NMP, Lidz CW, Miller FG, Nelson DK, Peppercorn J, Bluestone Rothschild B, Sankar P, Wilfond BS, Zimmer CR. (2007) Clinical Trials and Medical Care: Defining the therapeutic misconception *PLoS Med* 4:e324 doi:10.1371/journal.pmed.0040324.
- 11 Non- genetic examples include research on diabetes trials. Lawton J, Jenkins N, Darbyshire J, Holman R, Farmer A, Hallowell N (2011) Challenges of Maintaining Research Protocol Fidelity in a Clinical Care Setting: A qualitative study of the experiences and views of patients and staff participating in a randomised trial *Trials* 12:108.
- 12 General Medical Council (2010) *Good practice in research and consent to research*. [http://www.gmc-uk.org/guidance/research\\_guidance](http://www.gmc-uk.org/guidance/research_guidance) accessed 21.3.13; General Medical Council (2008) *Consent: patients and doctors making decisions together* Available at [http://www.gmc-uk.org/static/documents/content/Consent - English\\_0911.pdf](http://www.gmc-uk.org/static/documents/content/Consent_-_English_0911.pdf) accessed 21.3.13.
- 13 World Medical Association: *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*. 8th revision. Seoul, 2008 Available at: <http://www.wma.net/en/30publications/10policies/b3/17c.pdf>; *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Biomedical and Behavioural Research*. (1979) Available at: <http://www.csu.edu.au/learning/ncgr/gpi/odyssey/privacy/belmt.html> accessed 7.2.2013; *Nuremberg Code* (1947) Available at: <http://www.hhs.gov/ohrp/archive/nurcode.html> accessed 7.2.2013.
- 14 Exemptions from consent for the processing of personally identifiable clinical data are provided under the Data Protection provisions however, consent required under the *Data Protection Act* is not exhaustive as the common law also has a role to play. As far as consent for research purposes is concerned, there is a lack of consensus about the requirements of the common law for lawful processing, and the data protection principles (for fair processing) and their impact upon the consent processes, particularly where the principle of notification applies (where data collected for one purpose is used for another).

and the scope of the duty of care (both ethically and legally) of researchers who are not physicians.

## 4. The disclosure of findings generated by WGS undertaken in a clinical context

- 4.1 In the first section of this paper, we focused upon the characteristics of the variants that might be generated from WGS in research and clinical settings. In the rest of this paper, our focus is upon the normative framework that applies to the variants, namely the obligations to act on the information that has been generated, and in particular, to disclose information to professionals, patients/research participants.
- 4.2 As part of his professional responsibilities, the physician owes a duty of care to patients and this may involve informing them of risks arising from an intervention. In the case of WGS undertaken for clinical purposes the physician should inform the patients that the test may identify other genetic findings, which may impact on their (future) health. In turn, the patient may be presumed to have given implied consent to the disclosure of any such findings obtained as the result of the care and treatment they receive. The physician's duty will involve assessing the potential benefits and harms associated with disclosure of additional findings, informed by knowledge of the patient and the clinical context.
- 4.3 In contemplating whether disclosure of additional findings that are not directly related to the patient's presentation is in the patient's best interests, the physician might consider the following:
- The seriousness of the presenting problem and the nature of the other findings
  - Whether the finding represents a known clinical entity or risk factor or a finding that requires further investigation (e.g. variants of uncertain clinical significance, VUCS)<sup>15</sup>
  - Whether the finding has been validated to an acceptable standard<sup>16</sup>
  - The availability of any treatment/prophylaxis, and its likely success
  - Whether the finding is a risk factor for disease or represents a disease process
  - The age of the patient and co-existing morbidities and conditions
  - Prior knowledge of the patient's wishes
  - Custom, practice and precedent: how other professionals have handled the same finding in similar circumstances and the extent to which there is consensus about this approach.

---

15 Variants of uncertain significance, *i.e.* variants whose pathogenicity is unknown, have unproven clinical utility. Thus, the starting point ought to be that they should not be disclosed. However, in some cases it may be necessary to recruit further family members to determine whether an unknown variant is pathogenic or not and thus, it may be necessary to disclose this finding in order to investigate it further.

16 Ellard S et al. ratified by the Clinical Molecular Genetics Society Executive Committee (2012) *Practice guidelines for Targeted Next Generation Sequencing Analysis and Interpretation*.

- 4.4 In a clinical context, it is the professional obligations of **beneficence** and **non-maleficence** and the responsibilities of the physician that will drive the approach to the disclosure of additional findings, rather than the individual patient's autonomous wishes. In some circumstances these will require the physician to disclose and to investigate further if their significance is undetermined, as with a VUS.
- 4.5 The principle of **respect for autonomy**, in particular, supporting patient choice<sup>17</sup> has become increasingly important within a clinical context and is particularly pertinent if a patient has explicitly informed the physician at the start of an encounter that he or she does not want to be informed about additional findings. Nevertheless, in certain situations, physicians may override patient preferences if the duties of **beneficence** and **non-maleficence** require the physician to disclose information, such as where additional findings reveal a life threatening condition that is easily treatable. In other situations withholding information about additional findings may be justifiable, but in both cases the onus would be on the physician to justify such action if challenged in a court of law. Questions remain about how far these duties extend to 'at-risk' family members<sup>18</sup>.
- 4.6 The legal basis for (non)disclosure is established by existing professional practices and the *Bolam* standard<sup>19</sup> (as modified by subsequent case law), which questions whether the proposed behaviour is consistent with an 'ordinary competent man exercising that particular art' and 'in accordance with a practice of a competent body of professional opinion'. Thus, practice in different professional groups within health care (e.g. clinical geneticists, pathologists, other physicians) may develop according to prevailing professional standards and may vary between groups. Moreover, the professional responsibilities and obligations of different professional groups may interrelate and be iterative.
- 4.7 Approaches to the use of other novel technologies, such as imaging, may provide useful exemplars for developing disclosure practices in genomics. However, the rationale for distinguishing the disclosure of additional findings generated in genomics is far from clear. One aspect that may distinguish genomic data from abnormal imaging, haematological, microbiological or biochemical findings is that in most cases, a true finding will indicate a risk of disease rather than be indicative of a disease process<sup>20</sup>.
- 4.8 The significance of this distinction is that findings of any sort that reflect disease processes rather than risk of disease place the physician (and in some cases the researcher) under

---

17 Equity and excellence: Liberating the NHS Department of Health 2010. [http://www.dh.gov.uk/prod\\_consum\\_dh/groups/dh\\_digitalassets/@dh/@en/@ps/documents/digitalasset/dh\\_117794.pdf](http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_117794.pdf) accessed 31.1.2012.

18 Manolio T *et al.* (2013) Implementing genomic medicine in the clinic: the future is here. *Genetics in Medicine* doi:10.1038/gim.2012.157.

19 Based upon the case of *Bolam v Friern Hospital Management Committee* (1957) 2 All ER 118, [1957] 1 WLR 582.

20 Additional findings that may be unrelated to the presenting complaint may be found on clinical examination, by imaging the patient, or by way of an abnormal haematological, biochemical or microbiological test. In each of these instances the finding will either be a true positive or a false positive, since all tests have imperfect sensitivity and specificity. The clinician has a duty to be reasonably certain that it is the former (more so in the case of findings unrelated to the presenting complaint) before informing the patient. Non-genomic examples that raise the question of whether findings represent risk factors, or are diseases in their own right, include LDL cholesterol or hypertension.

greater obligation to return the result to the patient because the benefits and harms are less speculative. In the case of WGS and genetic variants, the presence of the variant normally<sup>21</sup> only provides evidence of disease risk and therefore, may be less compelling.

## 5. The disclosure of findings generated by WGS undertaken in a research context<sup>22</sup>

5.1 In the research context it is less clear what constitutes the best approach to disclosure. In part this is because the analytical validity of the variants that are generated in a non-clinically certified research laboratory is typically less robust, regardless of whether they are pertinent or incidental. Because of this, all variants found in a research setting that might possibly have an impact on a participant's health almost always require further validation<sup>23</sup>. This requires two elements to be satisfied: the analytical validity of the research findings requires confirmation and these results need to be assessed for clinical validity and clinical significance by competent and accredited professionals. Another reason for the lack of agreement or consensus is because the relationship between researchers and research participants is governed by a different set of duties and obligations than that between physicians and their patients. Consequently, when considering the nature and scope of consent to disclosure of potential findings generated during research we need to bear in mind that the relationship between the researcher and the research participant is primarily contractual<sup>24</sup>. This suggests that an *a priori* rule based framework setting out the basis for disclosure should be put in place for any research project. We list below a number of different frameworks<sup>25</sup> that could be adopted for disclosure of potential findings. These will have implications for the consenting process<sup>26</sup>.

- 
- 21 In some cases genetic testing is undertaken for diagnostic purposes, for example *BRCA1/BRCA2* testing to determine treatment options or Huntington's Disease testing to confirm that a patient is symptomatic.
  - 22 Please note in the following discussion of disclosure policies we are referring to all findings arising during the course of the research, both those that are pertinent to the aims of initial study and incidental (*i.e.* additional) findings that may emerge (see 2.3).
  - 23 Potential findings generated in research require confirmation and must be validated in a clinically accredited laboratory to accepted standards. This is because the findings may be of low diagnostic quality for technical reasons and their scientific and clinical interpretation requires a level of expertise that may not be available in a research setting. Although research results may be disclosed in advance of clinical validation, research participants must be informed of the need for validation.
  - 24 Meyer M.N (2008) The Kindness of Strangers: The Donative Contract Between Subjects and Researchers and the Non-Obligation to Return Individual Results of Genetic Research *Am J Bioethics* **8**: 44–50.
  - 25 Christenhusz GM, Devriendt K, Dierickx K (2012) To tell or not to tell? A systematic review of ethical reflections on incidental findings arising in genetics contexts. *EJHG* **21**: 248-255.
  - 26 For example papers by Wright Clayton E & McGuire AL (2012) The legal risks of returning results of genomics research. *Genetics in Medicine* doi: 10.1038/gim.2012.10; Affleck P (2011) Is it ethical to deny genetic research participants individualised results? *J Med Ethics* **35**:209-213; Bredenoord AL, Kroe HY, Cuppen E, Parker M, van Delden JM (2011) Disclosure of individual genetic data to research participants: the debate reconsidered. *Trends in Genetics* **27**: 41- 47; Knoppers BM, Joly Y, Simard J, & Durocher F (2006) The emergence of an ethical duty to disclose genetic research results *EJHG* **14**: 1170-1178; Wolf S, Lawrenz FP, Nelson CA, Kahn JP, Cho MK, Wright Clayton E et al. (2008) Managing incidental findings in human subjects research: analysis and recommendations. *J Law Med Ethics* **36**: 219-248; Wolf S, Crock BN, Van Ness B, Lawrenz F, Kahn J, Bescow LM et al (2012) Managing incidental findings and research results in genomic research involving biobanks and archived data sets. *Genetics in Medicine* doi: 10.1038/gim.2012.23; Kolleck R & Petersen I (2011) Disclosure of individual research results in clinico-genomic trials: challenges, classification and criteria for decision-making *J Med Ethics* **37**:271-275; NHMRC

5.2 The differences between frameworks take into account the clinical significance of the finding, its actionability and severity. It should be emphasised that the exact criteria for considering whether a variant is considered to be actionable or not and serious or not is context dependent and can only emerge during the process of seeking ethical approval for the study.

### 5.3 Non-disclosure of potential findings that might have an impact on the health of an individual

**FOR:** The ethical justification for non-disclosure of potential findings that might have an impact on the health of an individual relies on the principles of **non-maleficence** and **justice**. It is argued that disclosure could be harmful as the (psychosocial, economic, clinical) benefits remain unproven. Disclosure also has resource implications, not only does it require trained personnel to counsel research participants, but the findings themselves will require clinical validation.

**AGAINST:** Arguments against rely on the principles of **autonomy**, and **non-maleficence**. Disclosure may enhance individuals' **autonomy** through increasing their ability to choose what to know about themselves. Thus it is argued that non-disclosure of such findings may violate the research participants' **autonomy**, their ability to determine their future. Furthermore, non-disclosure may cause harm by overlooking information that may lead to early detection of disease risk, which may result in missed opportunities for prevention and treatment.

### 5.4 Disclosing only clinically significant findings that are severely and moderately life threatening AND clinically actionable

**FOR:** The prime reason for taking this approach is that the disclosure of clinically actionable findings is consonant with a professional's obligation to do no harm (**non-maleficence**), and it has the potential for reducing the risk of, or preventing, disease<sup>27</sup> (**beneficence**).

**AGAINST:** Arguments against include the lack of consensus about what is meant by 'clinically actionable' and 'severely or moderately life threatening' and which variants could, or should, satisfy these requirements. Disclosure may raise expectations amongst health professionals and patients about on-going obligations to report all findings that might have clinical implications, which in turn blurs the clinical/research boundary, undermines altruism and fuels the therapeutic misconception.

This approach also undermines the **autonomy** of research participants who do not want to be informed about any results, however, it could be modified to pay due respect to the

---

(2007) National Statement of Conduct in Human Research. <http://www.nhmrc.gov.au/book/chapter-3-5-human-genetics> accessed 6.5.2012.

27 Some have referred to the "rescue analogy" in making this point. A general example includes Singer P (1997) The Drowning Child and the Expanding Circle, *New Internationalist*, April, 1997. <http://www.utilitarian.net/singer/by/199704--.htm>. See also Ulrich M (2013) The Duty to Rescue in Genomic Research. *Am J Bioeth* 13: 50-51.

principle of **autonomy** by allowing the research participant to opt out of receiving findings, including those with clinical significance. The merit of not allowing any opt out is that it is clear and unambiguous and, therefore, potentially easier to implement and thus, less resource intensive. Finally, returning to arguments based on the principle of **justice**, all options which support disclosure of such findings will be more resource intensive. However, arguably in this instance there will be a trade-off between the resources needed for disclosure and subsequent follow-up and the potential decrease in morbidity and mortality that may result from early detection, prevention or treatment of serious life threatening disease.

## 5.5 Disclosing all clinically significant findings regardless of their severity AND actionability

**FOR:** This approach has the merit of basing disclosure decisions on clinical significance **alone** and does not require any independent judgements about actionability or severity. Ethically speaking, this puts the principle of **autonomy** to the fore<sup>28</sup>, because it enables individuals to have all the available information about variants that may have an impact on their health (and lives more generally) and the health of their offspring<sup>29</sup>, thereby maximising self-determination. As this disclosure policy reveals actionable (*i.e.* treatable or preventable) clinically significant findings it is also informed by the principle of **beneficence**, as individual research participants may benefit from knowing that they, or their putative offspring, are at risk of a preventable disease and therefore, will have the maximum opportunity to avoid or treat disease. Finally, this disclosure policy may have wider social benefits as it could assist the targeting of scarce healthcare resources towards disease prevention.

**AGAINST:** Arguments against disclosure of all potential clinically significant findings are based on the principle of **autonomy** and **non-maleficence**. Disclosure of potential findings that put individuals at risk of an untreatable or unpreventable and serious or life-threatening disease could cause them psychological (*e.g.* anxiety, depression) and social (*e.g.* stigmatisation, economic loss, discrimination) harm. In addition this may undermine their **autonomy** to not know information about themselves, although autonomy can be preserved in this scenario by including an opt-out clause as in 5.4. Finally, once again there is an issue of **justice** in resourcing the disclosure of any such findings. This policy compared to the one outlined in 5.4 would require more resources as potentially more variants would need to be disclosed (*i.e.* less serious variants) for fewer gains in terms of a reduction in morbidity and mortality, and in a publically funded healthcare system such issues must be considered.

---

28 Note that some research suggests that research participants may regard sequence information as having some use even if it is currently not interpretable. Facio FM, Eiden K, Fisher T, *et al.*, (2012) Intentions to receive individual results from whole-genome sequencing among participants in the ClinSeq study. *Eur J Hum Genet* doi:10.1038/ejhg.2012.179.

29 In contrast to the approach outlined in 5.4 the research participants in 5.5 may receive information about their carrier status for a number of untreatable diseases (eg. Huntington's Disease). While knowledge of one's carrier status may be considered harmful for oneself, these harms may be perceived as outweighed by the benefits this knowledge may have for one's offspring or other family members who are making reproductive decisions.



## 5.6 Disclosing all variants (regardless of severity, clinical significance and actionability)

**FOR:** This policy is justified by the assertion that the information obtained from WGS belongs to the research participants and researchers should not try to ‘second guess’ what they might want to know. At its most extreme, it proposes that the full genome sequence is returned to the research participant for him or her to do with it what he or she will.

**AGAINST:** There are a number of arguments against total disclosure. First, that such a policy would abrogate the researcher from all responsibility, and many would argue that by so doing the principles of both **beneficence** and **non-maleficence** are breached. Second, many variants may be difficult to interpret (VUS) and have uncertain clinical significance (VUCS) and disclosing these results without understanding their scientific or clinical significance could cause more harm than good by generating anxiety in research participants<sup>30</sup>. Third, the idea that the research participant ‘owns’ their sequence is problematic both ethically and at law. Finally, there is the resource issue as outlined in 5.4 - 5.5. The scale of the disclosure that might be needed with this approach might overwhelm both professionals and research participants.

## 5.7 Research participant chooses a disclosure policy

This seeks to maximise research participants’ **autonomy** by allowing them to choose which disclosure policy they prefer<sup>31</sup>. In its simplest formulation, each of the approaches in clauses 5.4-5.6 could include an opt-out clause, so that research participants could chose disclosure or non-disclosure<sup>32</sup>. Alternatively, research participants could be offered a range of choices, including each of the approaches outlined above, and also providing for the research participants to change their choices over time. Each of these options carries different clinical, technical and resource implications. These need to be addressed by stakeholders and policy makers alike.

**FOR:** The disclosure policies discussed above are really about choosing what type of variants should be disclosed along a spectrum of clinical utility, from high in 5.4 through high to moderate in 5.5, to high through low or non-existent in 5.6. Providing a choice maximises **autonomy**.

---

30 Vos J, Jansen AM, Menko F, van Asperen CJ, Stiggelbout AM, Tibben A (2011) Family communication matters: The impact of telling relatives about unclassified variants and uninformative DNA-test results *Genetics in Medicine* **13**:333-341.

31 See Hallowell *et al.*, who suggest that research participants’ autonomy could be maximised by using information technologies and web-based platforms to access different levels of research results; from the generic results of the research study (we found gene X in our study population), through the family’s results (we found gene X in members of your kinship), to personal results (we found gene x in you). Hallowell N, Alsop K, Gleeson M, Crook A, Plunkett L, Bowtell D, Mitchell G, The Australian Ovarian Cancer Study Group, Young M-A (2013) The responses of research participants and their next of kin to receiving feedback of genetic test results following participation in the Australian Ovarian Cancer Study (AOCS) *Genetics in Medicine* doi:10.1038/gim.2012.154.

32 Anastasova V, Blasimme A, Julia S, Cambon-Thomen A (2013) Genomic Incidental Findings: Reducing the Burden to be Fair *Am J Bioethics* **13**: 52-4. This paper describes how participant choice might inform the use of ethics filtering algorithms to allow the personalization of feedback preferences.

**AGAINST:** Providing too much choice could be overwhelming for research participants and may cause some anxiety, particularly if adequate support is not provided. Moreover, the documentation needed to support informed choice might be unduly complex and too technical for many<sup>33</sup>. Finally, providing a personalised approach to disclosure could be resource intensive, resulting in less money being available for the primary purpose of research.

## 6. Does the nature or application of WGS technologies change or influence these obligations?

6.1 The sequencing of the genome, the interrogation of the sequenced information and the interpretation of the data that are returned are three different phases of the sequencing process to which the phrase “sequencing of a whole genome” may be applied. A set of questions may be applied to each of these three phrases:

- **Sequencing:** How much of the genome will be sequenced, the whole genome, or the coding regions only (exomes)?
- **Interrogation:** How much of the genome will be interrogated, the whole genome, all exomes, or clinically targeted areas dependent on the clinical problem?
- **Interpretation:** How much of the interrogated data will be interpreted and by whom<sup>34</sup>?

6.2 The answers to these questions are crucial in informing our understanding of the nature of ‘whole genome sequencing’ as a test. The distinction between an ‘assay’ and a ‘test’ is fundamental to this; it allows us to regard the sequencing as the assay<sup>35</sup>, while the definition of the test<sup>36</sup> in any particular instance is reliant upon the purpose for which it is undertaken, which will, in turn, inform how the sequence is interrogated or interpreted. The assay may comprise either the entire sequence of the genome, or certain parts of it, and represents the initial step whereby the sequence of base pairs is determined. The interrogation essentially concerns the parts of the sequence that are to be analysed and may comprise only a subset of that sequence. This basic analysis must then be interrogated and interpreted to determine whether or not variants exist in the analysed sequence, and if so, whether they are of certain

---

33 Borgelt E, Anderson JA, Illes J (2013) Managing incidental findings: lessons from neuroimaging. *Am J Bioeth* **13**:2, 46-7. Palmour N, Affleck W, Bell E et al (2011) Informed consent for MRI and fMRI research: Analysis of a sample of Canadian consent documents. *BMC Medical Ethics* **12**: Doi:10.1186/1472-6969-12-1.

34 Moorthie S, Hall A & Wright C (2012) Informatics and clinical genome sequencing: opening the black box. *Genetics in Medicine* doi:10.1038/gim.2012.116; Ku C-S, Cooper DN, Polychronakos C, Naidoo N, Wu M & Soong R (2012) Exome Sequencing: Dual Role as a Discovery and Diagnostic Tool *Ann Neuro* **71**:5-14.

35 An assay is a method to analyze or quantify a substance in a sample (e.g. sequencing array).

36 We have previously defined a test as the application of an assay in a particular population, for a particular purpose in relation to a particular disease. (Zimmern RL, Kroese M (2007) The evaluation of genetic tests *J Pub Health* **29**:246-50). For each application of WGS it is therefore important to be clear about the nature of the disorder and of the population and, most importantly, the purpose of the test. For example, the use of the sequence of the entire genome in a population of infants with a presumed but undiagnosed inherited condition is a different test to its use in a population of adults with lung cancer to ascertain the types of mutation in a selected set of oncogenes notwithstanding that the same technology will be employed.



or uncertain significance, and whether they have any clinical relevance.

- 6.3 Another question concerns the appropriateness of using WGS technology: is it as good as established technologies (such as, targeted genetic tests or comparative genomic hybridization (CGH) arrays) at detecting certain types of pathological changes, for example, chromosomal re-arrangements, translocations and copy number variants? Some currently believe that certain clinically significant variants may be missed, even at 30 fold coverage and that Sanger sequencing of the relevant areas should be carried out following WGS<sup>37</sup>. If this is the case, then it might be more consistent, and appropriate, to refer to WGS as just the initial step in a more complex testing strategy. It is for these reasons that some clinicians believe that it is premature to replace existing technologies with WGS for some applications.
- 6.4 The principle of **justice** also takes on a particularly important dimension in WGS. The cost of the technology may mean that its benefits will not be equally distributed. How will equitable access to WGS be ensured? How will the opportunity costs in spending money on WGS technologies rather than other technologies or specialities be justified?<sup>38</sup>

## 7. Consent and the 100K Genomes Project

- 7.1 Consent to participation in the 100kGP and consent for disclosure of findings generated during clinical and research phases of the project are very different and need to be considered separately.
- 7.2 Consent to WGS as a clinical intervention is governed by the common law and requires that the patient is informed in general terms about the nature and purpose of the intervention. In addition, the physician has a duty to inform the patient of the broad benefits and risks involved, which in this case might include that in addition to pertinent findings WGS has the potential to reveal additional findings, namely, incidental findings. It might also include an explanation that these findings could require further investigation.
- 7.3 As noted in section 3 the guidelines for undertaking clinical research are underpinned by the principle of autonomy and emphasise the importance of obtaining fully informed consent for research participation. Such consent not only requires an understanding of the nature and purpose of the research intervention, but also the risks and benefits of research participation<sup>39</sup>. This usually includes a more comprehensive assessment of the risks and

---

37 Wright C (2013) £100M for whole patient genomes – revolutionising genetic diagnostics or squandering NHS cash? <http://www.genomesunzipped.org/2013/02/100m-for-whole-patient-genomes-revolutionising-genetic-diagnostics-or-squandering-nhs-cash.php> accessed 2.2.2013.

38 See Footnote 37

39 There is a longstanding ethico-legal debate about the requirements of informed consent in genomics research (Lunshof JE, Chadwick R, Vorhaus DB, Church GM (2008) From genetic privacy to open consent. *Nature Reviews Genetics* doi:10.1038/nrg2360) whether it should be a broad based generic consent to secondary analysis and use of DNA or whether it should be specific or targeted at particular uses (research studies). Hayden EC (2012) A Broken Contract *Nature* **486**:312-314; Allen C, Foulkes WD (2011) Qualitative thematic analysis of consent forms used in cancer genome sequencing. *BMC Medical Ethics* **12**:14. Indeed, some have argued that the challenges of obtaining sufficiently informed consent and data management are so great that it would be “irresponsible to

benefits of participating in research, including relevant wider societal impacts.

- 7.4 The timing of the consent that is sought for the research element of the 100kGP will have an impact on the form that this consent will take. For ethical, legal and pragmatic reasons we suggest that consent to research uses of the sequence collected during clinical encounters should be given in the clinical consultation. At this point the details of the research may be unknown. It may therefore be necessary to ask patients to give broad or generic consent for research uses of their DNA sequence.

## 7.5 Consent for disclosure of findings generated during clinical phases in the 100k genomes project

Consent for disclosure of findings generated during the clinical phases of the 100kGP is covered by the common law and was dealt with in sections 4.1 - 4.6 above. Consent to disclosure of these findings can be addressed at various time points, from before the sample is taken, to many years later, once results become available from later research using that sample or others<sup>40</sup>.

## 7.6 Consent to disclosure of findings generated during research phases

Consent to disclosure of findings generated during research phases of the 100kGP is potentially more ethically and legally complex and needs more thought and debate. As noted in 5.3-5.7 above there are a number of possible approaches to disclosure ranging from non-disclosure of any type of finding to full disclosure of the sequence data.

- 7.7 If the disclosure policy for the research elements of the 100kGP project is unknown, then obtaining a broad and generic consent to the possible disclosure of findings generated by research prior to the sample being taken will suffice. This should advise the participant of the possibility of findings being returned in the future.
- 7.8 We consider it likely that future research projects, including those using 100kGP data are likely to generate findings with clinical significance and are likely to disclose them on the basis that they confer significant risk and are clinically actionable. Indeed researchers seem likely to adopt a default policy of disclosing a well-defined subset of such findings<sup>41</sup> unless

---

pursue clinical applications of WGS". Sharp RR (2011) Downsizing genomic medicine: approaching the ethical complexity of genomic medicine by starting small. *Genetics in Medicine* **13**: 191–194. Others suggest a reasonable degree of consensus but highlight the need for extensive societal debate. Ayuso C, Millán JM, Mancheño M & Del-Ré R (2013) Informed consent for whole-genome sequencing studies in the clinical setting. Proposed recommendations on essential content and process. *Eur J Hum Genet* 1-6 doi: 10.1038/ejhg.2012.297. [Epub ahead of print].

40 New protocols are being developed that have reduced the time taken to use WGS for differential diagnosis from 4-6 weeks to 50 hours where speed is of the essence. See Saunders CJ, Miller NA, Soden SE, Dinwiddle DL, Noll A, Alnadi NA et al (2012) Rapid Whole Genome Sequencing for Genetic Disease Diagnosis in Neonatal Intensive Care Units *Sci Trans Med* **4**:1-13.

41 Evans JP, Rothschild BB (2012) Return of Results: not that complicated? *Genetics in Medicine* **14**:358-360; Berg JS, Adams M, Nassar N, et al., (2012) An informatics approach to analyzing the incidentalome *Genetics in Medicine* **15**: 36-44. Bredenoord AL, Onland-Moret C, Van Delden JM (2011) Feedback of individual genetic results to research participants: in favor of a qualified disclosure policy, *Human Mutation* DOI 10.1002/humu.21518; Berg JS, Khoury

patients explicitly OPT OUT of disclosure (see 5.4). This is consistent with an emerging consensus in many research settings.

- 7.9 If this is the case, then participants should be informed how their data is to be included in research, be warned of the possibility of re-contact and disclosure of findings in the future and detail should be given of the risks and benefits of disclosure, to the extent they are understood, before the sample is taken for sequencing. All of these issues should be included in the consent process.

## 7.10 Additional specific consent required by law

In addition to the contractual obligations described above, legislation such as the *Data Protection Act* (1998) and the *Human Tissue Act* (2004) provide for consent to be sought for certain uses of tissue or data<sup>42</sup>. Any combined consent that is sought should take account of the explicit requirements of the *Human Tissue Act* (to the extent that the proposed use is a Scheduled Purpose under that Act).

## 8. Recommendations

- 8.1 While we acknowledge that WGS information can be classified in various ways, we recommend that the 100kGP uses the framework set out in this document to determine what set of findings (pertinent or incidental) emerging from clinical or research sequencing are reasonably likely to have an clinical impact on an individual's physical or psychological health, and hence require disclosure or action.
- 8.2 The distinction between clinical and research activity should be made clear when clinical sequencing is raised in the 100kGP, and the ethical issues arising from the clinical use of WGS and any subsequent or interlinked research must be discussed at that time.
- 8.3 Consent for both the clinical and the research elements of 100kGP should be sought prior to samples being taken for clinical use. The form and the scope of such consent will need careful consideration.
- 8.4 It is our view that explicit informed consent for the disclosure of pertinent and incidental findings generated in research studies should be sought. The precise nature of this consent will be dependent on the disclosure policy ultimately adopted.

---

MJ, Evans JP (2011) Deploying whole genome sequencing in clinical practice and public health: Meeting the challenge one bin at a time. *Genetics in Medicine* **13**: 499–504; doi:10.1097/GIM.0b013e318220aab.

42 The HTA provides a regulatory framework for the use of human tissue. According to the *Human Tissue Act* (2004) consent would not be needed if tissue (from which DNA will be extracted) is held for the purpose of diagnosis and treatment of the person from which the bodily material was taken. However, if it is also to be used for re-research purposes, or for obtaining information about one person which may be relevant to any other person, (HTA Schedule 1 (part 1, paragraph 4)) then it would be prudent to seek consent for such purposes from all patients in the project.

- 8.5 We recommend that the 100kGP should adopt a policy of disclosing only research findings that are scientifically significant and have been assessed by a competent individual that are clinically significant AND severely or moderately life threatening AND clinically actionable. The operationalization of these terms will need to be determined for individual research projects. The consent procedure should also include a description of what types of findings will be disclosed, why these and not others; and also that any findings disclosed from research studies may need to be validated in a clinical laboratory.
- 8.6 We recommend that research participants in 100kGP studies should be permitted to opt out of disclosure, but acknowledge that in some circumstances opt out may be subsequently overruled. Research participants should be informed of this possibility when consent is initially sought.
- 8.7 We recommend that researchers explore the use of information technology to provide information to support the disclosure of research findings generated in 100kGP.







The PHG Foundation is a forward-looking genomics and health think-tank based in Cambridge, UK. Our mission is *making science work for health*. We work to identify the best opportunities for 21st century genomic and biomedical science to improve global health, and to promote the effective and equitable translation of scientific innovation into medical and public health policy and practice.

We provide knowledge, evidence and ideas to stimulate and direct well-informed debate on the potential and pitfalls of key biomedical developments, and to inform and educate stakeholders – policy makers, health professionals and public alike. We also provide expert research, analysis, health services planning and consultancy services for governments, health systems, and other non-profit organisations.

**phg**  
foundation  
making science  
work for health

PHG Foundation  
2 Worts Causeway  
Cambridge  
CB1 8RN

T +44 (0) 1223 740 200  
F +44 (0) 1223 740 892

ISBN 978-1-907198-12-0

[www.phgfoundation.org](http://www.phgfoundation.org)