

Presidential Commission for the Study of Bioethical Issues:

Request for Comments on Issues Related to Incidental Findings That Arise in the Clinical, Research, and Direct-to-Consumer Context

THE UNITED KINGDOM CONTEXT

Introduction

The PHG Foundation is a non profit making genomics and health think-tank based in Cambridge, UK. Our overarching purpose is to foster and enable the application of biomedical science, particularly genome-based technologies, for the benefit of human health. Among our specific objectives is the promotion of a social and regulatory environment that is receptive to innovation, without imposing an undue or inequitable public burden. The PHG Foundation has a particular interest in the way that new technologies, especially those relating to genomics, are translated within health services and in the impact of genomics upon clinical and public health services. As a multidisciplinary group of public health professionals, scientists, lawyers, social scientists, and those with ethical and health economics expertise, the PHG Foundation offers informed and expert comment on these issues.

General Comments

1. The PHG Foundation has a long standing interest in the incidental findings that might arise through genetic and genomic testing. Our work on the expansion of newborn screening reviewed the potential for large-scale public health initiatives to generate incidental findings of non-paternity or carrier status. Where screening can detect carriers of recessive diseases such as sickle cell anaemia, it remains a challenge to provide effective communication strategies that accurately inform participants of any health risks involved, without providing the potential for stigmatisation or discrimination.¹

Types of incidental findings

2. However, more recently the PHG Foundation has developed expertise in the potential for large-scale genetics or genomics testing to generate incidental findings in the sense of next-generation sequencing technologies being used to sequence and interrogate the entire human genome. The nature and likelihood of incidental findings arising through whole genome sequencing varies. In many research and clinical settings, the use of a whole human genome from one individual is supplemented by comparing it with samples from other family members, typically parents or more rarely siblings. In some clinical specialities, somatic and germline genomes are compared; in others, human and pathogen genomes are analysed. Thus there is potential for a number of different types of incidental findings:
 - Dominantly inherited, highly penetrant variants conferring a high risk of developing serious disease;

¹ *Expanded newborn screening: A review of the evidence*. Burton H, Moorthie S. PHG Foundation (2010). ISBN 978-1-907198-03-8.

- Recessively inherited variants conferring a high risk of having children with serious disease. This might affect reproductive choices that are made;
- Variants which are associated with a small increased risk of developing a common complex disease (such as many forms of cancers, cardiac conditions, diabetes, etc);
- Variants of unknown significance;
- Evidence of mis-attributed paternity;
- Evidence of various degrees of consanguinity.

The potential for Whole Genome Sequencing to generate incidental findings

3. The PHG Foundation undertook a comprehensive project to explore the implications of whole genome sequencing for health in the UK which reported in 2011.² Our focus in this report was the clinical implementation of next generation sequencing technologies and whole genome sequencing technologies for health services, particularly within the UK National Health Service. Chapters 8 and 11 of the report acknowledged the potential for incidental findings to be generated, and suggested a variety of relevant factors and policy approaches.
4. We concluded (at *Next Steps in the Sequence* page 5) :

'We do not believe that the NHS has an explicit duty of care to screen an individual's genome or offer tests beyond evidence-based analyses relating to the specific clinical or population health purpose(s) consented to by the patient. Moreover it is advisable to minimise incidental findings where possible; health care professionals should not have an obligation to feedback findings that do not relate to the clinical question, except in cases where they are unavoidably discovered and have high predictive value. It follows that the NHS does not have an obligation to provide patients with their raw genome sequence data for further analysis outside of the NHS. We make no judgement here about whether the individual should be able to purchase and analyse their genome sequence independently; however, if this course of action is pursued, the NHS should provide follow-up advice and care only when additional findings are considered to be of significant clinical relevance in that individual.'

Research Initiatives in the UK

5. There are a number of important research projects underway in the UK which are exploring the ethical basis for managing incidental findings generated from genetic and genomic testing. These projects vary in type and scope. One of the most significant is the Deciphering Developmental Delay project (DDD project) being implemented by the Wellcome Trust Sanger Centre in Cambridge (<http://www.ddduk.org/>). This project aims to use exome sequencing to identify a genetic cause of developmental delay in children where other targeted genetic tests have failed to identify a cause. Clinicians within clinical genetics services in the NHS are recruiting families to this project. Genome sequencing, interrogation and interpretation are done by researchers at the Wellcome Trust Sanger Institute. This project has an explicit policy of not feeding back any incidental findings that

² PHG Foundation (2011) Next steps in the sequence: The implications of whole genome sequencing for health in the UK.

are generated by the analysis (including findings of non-paternity). This policy was adopted from the outset, and is stated in the patient information sheets supplied to research participants. However, wider stakeholder and public attitudes are being canvassed as part of the DDD project, including an accessible video and [questionnaire](https://survey.sanger.ac.uk/genomethics/) (<https://survey.sanger.ac.uk/genomethics/>). The lead researcher on this part of the project is Dr Anna Middleton.

6. The UK Government and leading research funders are also implementing two cohort studies. The first, the UK Biobank, has recruited 500,000 healthy volunteers aged between 40-69 years between 2006-2010. Baseline medical screening tests have been carried out, including blood pressure and cholesterol testing. Results from these tests are being fed back to participants. Smaller cohorts are being invited for specialist imaging (MRI), with a pilot study of MRI scans of brain, heart and abdomen being started later in 2013. The possibility of inviting a small cohort for whole genome sequencing is also under active review.³
7. More recently the UK Government has announced its intention to establish a project to sequence 100,000 genomes focusing upon cancer, rare diseases and infectious diseases. Three working groups were set up to review specific aspects of the project, concentrating upon scientific aspects, ensuring a valid consent and managing incidental information arising from genome sequencing.
8. In advance of the details of this initiative being finalised, the PHG Foundation published a discussion paper *'Managing incidental and pertinent findings from WGS in the 100,000 Genomes Project'*.⁴ This paper explores the terminology of 'incidental' and 'pertinent' findings in genetics and genomics in research and clinical care. It reviews the relevant ethical and legal principles, differentiating between research and clinical settings. Finally it proposes a framework for disclosing different classes of finding, and makes a number of recommendations that are extremely relevant to the scope of the Presidential Commission's enquiry. These recommendations are as follows:
 - *'Consent for both the clinical and the research elements of the 100KGP should be sought prior to samples being taken for clinical use. The form and the scope of such consent will need careful consideration [8.3].'*
 - *'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' [8.4]*
 - *Only research findings that are scientifically significant, and have been assessed by a competent individual as being clinically significant AND severely or moderately life-threatening AND clinically actionable should be disclosed.[8.5]*
 - *The consent process should include a description of what type of findings will be disclosed, and the rationale for their disclosure (and not others). It should also address the need for further validation in a clinical laboratory [8.5]*

³ See for example the UK Biobank Participant Newsletter 2013 available at <http://www.ukbiobank.ac.uk/wp-content/uploads/2013/04/2013Newsletter-text-only.pdf> (accessed on 12.6.13)

⁴ Available at <http://www.phgfoundation.org/reports/13799/> (accessed on 13.6.13)

- *Research participants should be permitted to opt out of disclosure [8.6]. If there is a chance that in exceptional circumstances that this right could be overruled, this possibility should be addressed in the consent process.'*

Clinical implementation of WGS sequencing in the UK

9. Centres of expertise are beginning to implement WGS technologies within various clinical services in the UK. This is not being done systematically. However WGS is being trialled in the context of infectious diseases and in paediatrics to identify causes of learning delay, although, to our knowledge, this is not yet being used in routine clinical care. There are also many instances of next generation sequencing being introduced as a replacement technology on grounds of cost-effectiveness to sequence panels of genes implicated in specific inherited conditions.
10. National professional guidance has not yet been developed within the UK to guide the implementation of WGS in clinical practice. The PHG Foundation is undertaking a project to systematically analyse the ethical, legal and social issues which are likely to arise. This project comprises a set of four multidisciplinary stakeholder workshops over the next 18 months to address different dimensions of the clinical implementation process. The following topics will be examined:
 - i. Empirical research on ethical, legal and social issues arising from clinical implementation of WGS/WES technologies
 - ii. Ethical, legal and social aspects arising from the interface between research and clinical care in genetics and genomics
 - iii. The proposed patient pathway
 - iv. Implications for policy makers and other stakeholders.
11. In this work we expect to take account of the evolving debate across the clinical genetics specialty about how incidental findings should be managed in clinical settings. One influential professional body, the American College of Medical Genetics and Genomics (ACMG) have characterised this debate as being between the genetic libertarians, who advocate that individuals should be able to access their entire genetic sequence, through to genetic empiricists who mandate non-disclosure on the basis that evidence of benefit is not sufficient.⁵ The ACMG advocate that where WGS technologies are offered within clinical settings, that a supplementary set of genetic variants are sequenced, interpreted and reported to the referring physician, who has ultimate responsibility for disclosing results to the patient. These variants have been identified on the basis of their clinical utility, i.e. on the basis that they are variants that confer substantial risk of harm for a serious disease which is clinically actionable. Furthermore, the ACMG argues that these variants should be sequenced irrespective of the age of the patient. One of the most controversial elements of these recommendations is the argument that access to WGS in clinical settings should be contingent on prospective patients agreeing to the sequencing and disclosure of this additional set of variants.

⁵ American College of Medical Genetics and Genomics (2013) ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing. Accessed on 11.6.13 at http://www.acmg.net/docs/ACMG_Releases_Highly-Anticipated_Recommendations_on_Incidental_Findings_in_Clinical_Exome_and_Genome_Sequencing.pdf

12. The ACMG have published an additional clarification.⁶ The major justification offered in this statement is that *'not reporting a laboratory test result that conveys a near certainty of an adverse yet potentially preventable medical outcome would be unethical.'*
13. In contrast, the European Society of Human Genetics (ESHG) advocates a more comprehensive and measured approach which is in line with existing European professional guidance on genetic testing in children⁷, and genetic testing more broadly⁸. Targeted sequencing and analysis and filtering of the results to avoid unsolicited or uninterpretable findings is their preferred approach. However, if a whole genome approach is justified and proportional (on the balance of benefits and harms) [3], the ESHG suggest that a protocol should guide the reporting of unsolicited genetic findings. *'If the detection of an unsolicited genetic variant is indicative of serious health problems (either in the person tested or his or her close relatives) that allow for treatment or prevention, in principle, a health-care professional should report such genetic variants.'*[4]
14. The ESHG stress the need for a multidisciplinary approach, so that stakeholders can share experiences and establish relevant guidelines at local, national and international levels. They highlight in particular the need for specific guidelines on informed consent, testing of children, recontact and the interface between clinical and research settings. Thus their approach is more consensual, building on existing policies and practice.

COMMENTS AND RECOMMENDATIONS OF THE PHG FOUNDATION

15. With these contextual issues in mind, we offer the following comments. These issues are addressed in more detail in our Position Statement - *Managing incidental and pertinent findings from WGS in the 100,000 Genomes Project.*⁹

Definition of Incidental Findings: The prerequisite for scientific and clinical validation

16. In our view, 'incidental findings' are those findings that have two defining characteristics:
- a. They should be findings that are ***scientifically significant*** by which we mean that there is robust statistical evidence of a relationship between a genomic variant, usually a genetic variant, and a particular phenotype;
 - b. They should be findings concerning a patient, research participant or consumer that may, or may not, have potential health implications and clinical significance, that are discovered during the course of a clinical, research or consumer-instigated investigation, but *are beyond the aims of the original test or investigation.*

⁶ American College of Medical Genetics and Genomics (2013) ACMG

http://www.acmg.net/docs/Incidental_Findings_in_Clinical_Genomics_A_Clarification.pdf

⁷ Such as British Society of Human Genetics (2010) Report on the Testing of Children, Birmingham. Available at: http://www.ethox.org.uk/Documents%20and%20images/GTOC_2010_BSHG.pdf (accessed 11.6.13)

⁸ ESHG Public and Professional Policy Committee (2013) Whole-genome sequencing in health care: Recommendations of the European Society of Human Genetics *European Journal of Human Genetics* 21, 580-584;doi:10.1038/ejhg.2013.46

⁹ See footnote 4 *op. cit.*

General considerations in defining policies on return of incidental findings

17. The scope of the Presidential Commission's enquiry is very broad. Our comments focus upon the disclosure of incidental findings arising from genomic technologies in research and clinical care. Additional issues apply to the disclosure of incidental findings in the context of direct-to-consumer tests. Here the relationship between provider and consumer is a contractual one. We have argued elsewhere that the ethical principles governing direct-to-consumer genetic tests should be based upon respecting the autonomy of the consumer through safeguarding principles of transparency and accountability.¹⁰
18. We also distinguish incidental findings generated from imaging from incidental findings generated through genetics or genomic testing, since on imaging, findings tend to be indicative of a disease process, rather than indicate a risk of disease. Whilst the ethical principles underpinning these tests are the same (i.e. beneficence and non-maleficence) it may be more difficult to make these assessments in the case of predictive tests. Thus radiological imaging is not, in our view, an apt analogy for genetics and genomics tests.
19. Any policy on managing incidental findings should be developed on a project by project basis, taking account of the context of the application (i.e. research, clinical or direct to consumer) with a view to developing a proportionate policy that weighs the relative risks and benefits. Thus we argue that the key considerations for managing incidental findings in the context of genetics and genomics include:
 - a. The context for the disclosure (e.g. whether it is clinical or research; or whether the primary purpose is for clinical care or delivery of a population based screening programme)
 - b. Whether the finding is a 'true' incidental finding or arises as a result of opportunistic screening (such as the example described in paragraph 11 above)
 - c. Explicit consent should, as a general rule, be sought for any opportunistic screening that is done as an adjunct to testing for a primary clinical or research purpose, and also for the disclosure of any incidental findings that result from that opportunistic screening.

Specific considerations

20. In response to the specific enquiries raised by the Presidential Commission:-
 - **Information about the likelihood of incidental findings arising in large-scale testing**

In our view, the ethical principles underpinning the management of incidental findings emerge more clearly if a robust definition of 'incidental findings' is systematically applied across applications. Thus as described above in paragraph 16, we favour a definition that regards incidental findings as those which are scientifically significant and beyond the aims of the original test or investigation. This definition excludes variants of

¹⁰ EU Proposals for Revising Directive 98/79 of the European Parliament and of the Council of 27 October 1998 on *In Vitro* Diagnostic Medical Devices. Response from the PHG Foundation to the tabled amendments to draft EU regulation on *in vitro* diagnostic medical devices (IVDDR)

unknown significance, and those variants that are generated through opportunistic screening.

- **What should individuals be told *before* testing?:**

All individuals should be informed in **general terms** about the following:

- The theoretical potential for incidental findings to be identified
- The likelihood of incidental findings being detected in their case
- The harms and benefits associated with disclosure, for themselves and if relevant, for family members
- The available choices (e.g. to accept or refuse disclosure or further qualify this choice in some way, or to revisit the issue at a later date)
- The processes involved (e.g. involvement of other professionals such as clinical geneticists or GP's)
- The further steps which might be taken if an incidental finding is detected and disclosed.

- **The duties and obligations to *actively look* for findings:**

We acknowledge that genomic sequencing and interpretation is at an early stage of its development. Professional best practice in this area has not yet been fully articulated. In part this is because the frequency of genetic variants within populations is not completely understood, and thus it may be difficult to assess the likely pathogenicity associated with particular genetic variants. Many uncertainties remain: given these uncertainties, we reject the claim that it would be unethical NOT to seek genetic variants that confer serious but treatable disease.

Our view is that the process of actively sequencing and interpreting known variants is a form of *opportunistic screening*, whose benefit in the general population is as yet unresolved and that to classify this practice as the return of incidental information is misleading. We suggest that there is therefore no obligation to actively LOOK FOR certain incidental findings. If however this is offered, it should be made explicit that this practice supplements clinical care (or research), and unless there is exceptional justification, access to clinical care (or research) should not be contingent upon agreeing to the results of testing such a panel of additional variants being returned.

- **Best practices for determining when and how incidental findings ought to be returned**

We have suggested some wording in previous sections. To summarise we suggest that it may be acceptable to offer to disclose incidental findings relating to serious diseases, which are actionable in both clinical care and research provided that:

- The possibility of disclosure is addressed in advance of testing

- The patient/participant is able to refuse or opt out of disclosure if they wish
 - There are systems and structures in place to ensure that any findings potentially satisfying the above criteria which fall below established clinical standards, are further investigated, and where possible, validated for clinical use
 - That research participants/patients have access to appropriate clinical expertise in order for them to be able to address the health issues raised by these findings, including wider implications for other family members.
- **The acceptability of “no return” policies**

At present, there is a deficit of empirical evidence concerning the potential harms and benefits of disclosing incidental findings in genomics and genetics. For this reason, we consider that “no return” policies are acceptable, and often advisable, particularly in research settings. This is a very quickly evolving area and much empirical work is underway. For this reason, we suggest that policies on incidental finding should be developed with input from all relevant stakeholders, including research participants or patients, and that they should be reviewed regularly.

If you would like further clarification or amplification from us in respect of any areas of this briefing note, please let us know.

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