

# Realising genomics in clinical practice

December 2013

**Interim report**

# Acknowledgements

We would like to thank all the delegates to Workshop 1 for contributing their knowledge, experience and insight to the discussions outlined in this report.

# Background

This first workshop of the Realising Genomics project was held on 9 and 10 July 2013, and focused on the ethical, legal and social issues (ELSI) raised by the implementation of WGS/WES in clinical practice.

## Past projects

The PHG Foundation undertook a comprehensive project to explore the implications of whole genome sequencing (WGS) for health in the UK which reported in 2011<sup>1</sup>. Our focus in this *'Next Steps in the Sequence'* report was the clinical implementation of next generation sequencing technologies and WGS for health services, particularly within the UK National Health Service. Chapters 8 and 11 of the report acknowledge the potential for incidental findings to be generated, and suggest a variety of relevant factors and policy approaches, including that where possible targeted sequencing be used and the generation of incidental information be kept to a minimum.

## The Realising Genomics in Clinical Practice project

The Realising Genomics (RG) project follows on from this earlier work. In the RG project we focus on the ethical, legal and social issues that are likely to arise from the clinical implementation of next generation sequencing (including WGS and whole exome sequencing (WES)). These issues are highly relevant to the UK government's 100,000 Genomes Project as it gets underway. The RG project comprises a set of four multidisciplinary invited stakeholder workshops held over 18 months to address the most problematic and important dimensions of the clinical implementation process, supported by conceptual work:

i. **Empirical research on ethical, legal and social issues arising from clinical implementation of WGS/WES technologies (July 2013)**

Researchers from around the world including bioethicists, social scientists and lawyers met to consider the preliminary findings of their research. This generated discussion of relevant ethical, legal and social issues including: the need for new approaches to gaining informed consent, the need to develop guidelines for the handling of unexpected results, and the changing nature of the research-clinical interface.

ii. **Ethical, legal and social aspects arising from the interface between research and clinical care in genetics and genomics (December 2013)**

Research and clinical activities have been viewed as distinct activities conferring separate ethical and legal rights, duties and obligations upon different actors. In this workshop we will explore whether it is necessary or desirable for the boundary between research and clinical care to be maintained when genomic technologies are implemented, and consider alternative approaches.

<sup>1</sup> PHG Foundation (2011) *Next steps in the sequence: the implications of whole genome sequencing for health in the UK*.

iii. **The patient pathway (spring 2014)**

The introduction of genomic technologies will impact upon existing patient pathways and the purpose of this workshop is to explore how these patient pathways may need to be revised with the implementation of WGS technologies, exploring the ethical, legal, social and practical issues that might arise.

iv. **Implications for policy makers and other stakeholders (summer 2014)**

In our final workshop we plan to build upon the findings from previous workshops and formulate policy recommendations and guidelines involving a wide range of stakeholders.

These workshops will be supplemented by a range of outputs including interim briefings, policy documents and peer-reviewed publications throughout the life of the project.

**Workshop 1 Empirical research**

The first of these workshops, on empirical research on ethical, legal and social issues arising from the clinical implementation of WGS/WES technologies, was held on 9-10 July 2013 at Madingley Hall, Cambridge.

Most delegates were invited on the basis that they were actively engaged in research on the clinical implementation of genomic technologies. Delegates came from Europe and USA/Canada. This report summarises key points arising from the presentations, the substantive discussions, and the main themes that emerged. The discussions reflect the interests and expertise of individual delegates and are not necessarily comprehensive or representative of the views of all stakeholders. However, they provide an overview of issues which might be helpful to policy makers.

A list of delegates is attached at Appendix 1.

On day 1, delegates were asked to present preliminary research findings, followed by questions and discussion. As the workshop was residential there was ample opportunity for informal discussion and debate.

On day 2 delegates were asked to consider the question "What in your view is the main ethical, legal or social issue/challenge raised by the implementation of WGS technologies into clinical care?" in the light of the presentations made on day 1.

# Day 1 Reflections on current practice

On day 1 delegates presented preliminary research findings, followed by discussion about the duties and responsibilities of researchers and clinicians.

Presentations were made on the following topics:

- The use of WGS/WES in a research setting, with a view to clinical implementation
- Ethnographic and qualitative research of existing clinical practice to help determine the challenges that might be presented by the introduction of whole genome sequencing
- The strategies used by clinicians to manage uncertain, unexpected or incidental findings when they arise
- Research on the appropriateness of consent procedures for the return of results after diagnostic exome sequencing
- Qualitative research concerning attitudes to, and expectations of, genomic technologies, including WGS
- Attitudes of health professionals, ethics committees, researchers and families to the return of incidental findings
- The management of the return of clinically significant findings from a research project (the UK 10K Project).

Presentations provided evidence that clinicians use a variety of different terms to describe findings that fall outside the primary purpose of testing, including: 'unexpected', 'unsolicited' and 'incidental' findings. There is a lack of consensus about the use of these terms, suggesting their meanings are evolving. For example, incidental findings might be used to describe variants of unknown significance that are related to the primary clinical enquiry.

Speakers also reported that clinicians sometimes do not warn their patients before testing that the use of genomic technologies may generate 'unexpected' findings although, when questioned, most clinicians state that this should be a component of the consent process.

### Duties and responsibilities of researchers and clinicians

There was a lot of debate about the extent to which the setting for undertaking WGS (research or clinical) might generate different duties, responsibilities, and expectations amongst healthcare physicians, patients, research ethics committee members and other stakeholders. Two ethical principles were identified as being paramount in both research and clinical settings – respect for autonomy and beneficence. It was agreed that in a research setting, respect for autonomy should prevail. However, in practice, the boundary between the two activities is becoming increasingly blurred. Workshop participants discussed various strategies for managing this ambiguous relationship, including developing a hybrid model which might incorporate elements of the ethical principles underpinning both activities.

This topic will be taken forward in Workshop 2. Some of the presentations also highlighted the potential for individual patient choices to be overruled. This aspect is discussed further below.

# Day 2 Emerging themes

Delegates were asked to consider the question “What in your view is the main ethical, legal or social issue/challenge raised by the implementation of WGS technologies into clinical care?” in the light of presentations made on day 1.

This task involved asking delegates to extrapolate from the research findings presented during the workshop, and to use their own expertise to identify the most pressing issue or challenge that might need to be addressed. Delegates identified 13 key themes and 18 subsidiary themes from the presentations and discussions covering seven key areas. These were prioritised and grouped as a collective exercise and three overarching topics were identified for discussion in small groups. The findings of each group were then fed back in a final plenary session. (Figures in brackets indicate the number of times the issue was raised):

## a) Datasets (7)

The large datasets of genetic variants generated by these technologies will need interpretation if they are to be used within the clinic. Managing the complexity of data and ensuring that there are mechanisms to handle the large datasets generated will be a challenge, particularly in rare diseases. Bioinformatics pipelines need to be developed and managed in a way that allows meaningful data feedback to clinicians with the ultimate aim of guiding clinical interventions. These bioinformatics pipelines will need to be capable of grouping and re-analysing variants with uncertain clinical significance as further phenotype-genotype relationships are elucidated. There should be clarity about the current clinical utility and levels of uncertainty linked to genomic results. The processes and tools that are developed will need to manage this uncertainty and allow for personalised approaches.

Currently the NHS does not have the capacity to store the volume of genomic data likely to be generated by WGS and WES. Policies are urgently needed to determine the relative merits of storing whole exome and whole genome sequences for subsequent reanalysis when new disease causing variants are found, as against re-sequencing.

## b) Trust and the consent process (7)

There is a need to develop consent processes that are meaningful and protect patient autonomy whilst also not undermining the professional’s ability to discharge their duty of care. In order to maintain trust in the consent process it will be important to be explicit about potential differences in perspective between the health care professionals and their patients. This might include:

- When consent or refusal from a patient can be overruled
- The extent to which patients have the right to refuse clinical information for themselves or for their children
- How far the individual can control sharing of their data (whether identifiable or not)

- Whether a prerequisite for receiving WGS or WES should or could be the sharing of data with individuals who are not entitled to access identifiable patient data on clinical grounds. This might include sharing data with researchers or others.

This could be done through developing exemplar consent processes<sup>2</sup>. It is also vital that the public's trust is maintained and expectations managed, especially the expectations of those involved in research, through the responsible and realistic communication of the risks and benefits of undergoing genomic testing.

### c) Clinical research boundary (3)

Evidence from the workshop suggested that the boundary between research and clinical practice is losing its current distinction with the use of genomic technologies. This is significant because different ethical frameworks govern research and clinical care. For example, the duty of care of researchers to research participants differs from that owed by clinicians to their patients. These ethical obligations have implications for ongoing care, including the return of findings from research or care, and the obligations for follow-up or re-contact.

The impact of genomics on the clinical/research boundary will be examined at Workshop 2 with the aim of clarifying the extent of this change, articulating the ethical principles which apply and ultimately formulating consensus guidelines/standards for best practice.

### d) Education (3)

There is a pressing need to educate and inform health care professionals, and patients on the complexity of genomic tests and their results (including variants of unknown significance, incidental findings and carrier status) in advance of their being introduced into mainstream medicine. This complexity must also be reflected and incorporated into the discussion on consent, empowering patients and their relatives to make truly informed decisions. Training a wide range of professional groups is also required to ensure they have the confidence and ability to communicate these complex issues to their patients in ways they can understand and act upon. This is likely to extend beyond clinical genetic specialists to all those likely to be ordering and handling genomic test results in the near future. The eventual aim would be a general improvement in genetic literacy.

### e) Resources and equity of access (2)

In a climate of cost containment, there is a need to re-examine how to prioritise allocation of health care resources so that this technology ultimately results in patient benefit. Workshop participants aspired to the view that innovation should result in technologies that improve care, thus where possible, equity of access should be ensured. Once technologies are adopted by health services, robust and objective criteria for commissioning should be developed.

<sup>2</sup> Exemplar consent processes will be developed as part of the Realising Genomics programme in Workshop 3

#### f) Risks associated with opportunistic screening (1)

The comprehensive nature of WGS/WES enables the investigation of a genome for the presence of genetic variants that are unrelated to the presenting clinical problem. For these variants, testing constitutes a form of opportunistic screening of asymptomatic individuals, with the benefits being more marginal and the risks (such as overdiagnosis) being greater, and poses a different set of questions and responsibilities/obligations to diagnostic testing.

The PHG Foundation is undertaking additional work to explore the policy implications of offering genomic opportunistic screening. Policy development will need to address the potential impact of these tests, the benefits and burdens to individuals and to society more generally, any safeguards that should be imposed and the wider acceptability of this type of screening.

#### g) Children (1)

There are particular challenges in returning genomic information relating to children, particularly those that are unrelated to the clinical phenotype. Careful consideration needs to be given to how to balance the right of the child to make autonomous decisions for their self in the future, as against the need to act in the child's current best interest.

#### h) Cross-cutting issues

Many delegates noted that there was a lack of conceptual clarity in a number of key aspects such as the distinction between 'pertinent' and 'incidental' findings and in 'testing' and 'screening'. There is also a need to distinguish between existing medical problems, genetic predisposition and benign traits. Thus the requirement for conceptual clarity was identified as an overarching issue. It was also noted that there was a need for additional psychosocial research to inform how risk results might be interpreted and acted upon in clinical and research settings and to assess what impact the use of these technologies might have on the patient/health care professional relationship.

These issues were grouped into three overarching themes which were taken forward for discussion in small groups. These were:

- 1 **Scale** (*i.e.* how are genomic technologies likely to be implemented within clinical settings? How will they be translated from research to clinical settings?):
  - Governance
  - Technology and social media
  - Translation
  - Managing patient expectations
  - Securing a meaningful consent
  - How to balance benefits, harms, autonomy and justice?

2 **The requirement for conceptual clarity** (*i.e.* what is current practice within research and clinical arenas? Are there areas of practice and proposed implementation that require greater clarity and transparency?):

- What is the vision for the use of these technologies?
- How should clarity about the nature of the activity be achieved?
- The need for transparency (including the potential for incidental findings to be generated)
- The need to avoid coercion
- How to balance benefits, harms, autonomy and justice?

3 **Operational issues** (*i.e.* what operational issues are likely to be important when implementing WGS/WES for clinical purposes?):

- Access/equity
- Prioritisation
- Securing a meaningful consent
- Managing expectations
- Childhood testing
- Educational issues
- How to balance benefits, harms, autonomy and justice?

# Discussion

The 1st Realising Genomics Workshop provided a basis for understanding the ethical challenges raised by the clinical implementation of WGS/WES. In particular, the workshop generated a comprehensive overview and prioritisation of emerging issues.

At the meeting, we categorised these into three types – scale, conceptual clarity and operational issues. The rich debate that emerged from these three groups has been used to guide future workshops and outputs from the project.

## Scale Group discussion

Genomic technologies are challenging in scale in a number of ways. The results that are generated are likely to be heterogeneous being diverse in character and content; if entire genomes are sequenced and retained, this will involve the acquisition of around three gigabases of DNA, assuming 100% coverage; if only exome data is collected covering 20,000 genes, this still comprises around 30Mb of data despite representing only 1% of the entire genome; even if testing is targeted, these technologies comprise simultaneous acquisition of sequencing information about multiple genes and conditions; they also allow novel applications. These include the systematic evaluation of healthy volunteers, population based carrier screening or pre-conception testing, and the opportunistic screening of individuals presenting for clinical care. However, whilst the technologies facilitate these applications, the decision to use them for these different purposes must be deliberate.

The scope of applications and the heterogeneity of the data (from highly predictive to variants conferring no additional personal or clinical utility) means that the utilisation of WGS is both 'revolutionary and mundane'. This has implications for how these technologies might be governed and requires a governance structure that is anticipatory, reflexive and proportionate.

Two main frameworks were discussed. The first sorted data by type and the second by application:

- 1 **Type:** *e.g.* genetic, medical or non-medical
- 2 **Application:** *e.g.*
  - Diagnosis (uses a medical paradigm grounded in patient benefit)
  - Screening (uses a medical paradigm grounded in patient benefit)
  - Generating medical information such as carrier testing for reproductive choices (a clinical genetics paradigm grounded in patient choice and autonomy)
  - Research

The second framework applied governance at the level of the dataset/sample. This was thought to be preferable on the basis that it was more flexible and dynamic, allowing simultaneous multiple uses. Moreover patients could be

put at the centre of the process, and might choose to exert a variable amount of control depending upon the application. For example, patients could exert more controls for research and less for applications such as public health, where arguably public interest might legitimately override individual patient choice in some circumstances. In both frameworks, patients and participants need to have a broad understanding of the potential uses to which their data might be put and opportunities to re-consent if the sample is used for additional applications. Patients also needed to be confident that the data was held securely, whilst being capable of being shared. It was noted that the 100,000 Genomes Project might be used as a mechanism to test the feasibility of alternative models of recruitment and consent.

### Conceptual Clarity Group

The need for conceptual clarity is a cross cutting element that is relevant to every aspect of clinical implementation. There needs to be transparency about what technology is utilised (*i.e.* WGS or WES). This should include discussing issues such as coverage and the added value of using this technology rather than other alternatives. There should also be transparency about why a technology is being used, such as whether for diagnostic or screening purposes, and the nature of the drivers (*e.g.* for additional health benefits or for non-health reasons such as promotion of investment or employment). It is also important to address the setting – whether the objectives for use are primarily for clinical or research purposes, bearing in mind difficult boundary issues.

The indiscriminate application of genomic technologies increases the potential for unexpected findings. There needs to be more clarity to distinguish between different types of finding and more consistency in the way these terms are used in various settings:

- 1 Pertinent findings (that are relevant to the primary clinical question)
- 2 'Truly incidental' findings – that are generated as an inevitable consequence of (1) above
- 3 Secondary or opportunistic findings – that are sought purposefully as an adjunct to (1) above, such as the ACMG's list of 56 variants

The standards of evidence required for each of these three types of findings are very different. There is a need for terminology that is more accessible to patients (*e.g.* to distinguish between data and information).

The requirement for conceptual clarity about the technologies being used, the justifications for their use, the classification of the findings that result and their ongoing management led to the following conclusions:

- There needs to be more transparency about how raw data is interpreted to become informative, making the difference between acquisition and analysis
- There might need to be different thresholds for reporting results according to whether the test is diagnostic (where the patient seeks help

for an existing complaint) or for screening (where the physician offers an intervention in order to determine risk of developing future disease). These different thresholds might be needed to address potential ascertainment bias arising from testing patients who are already symptomatic

- There needs to be more work to determine the feasibility of targeting the interpretation of WGS raw data to minimise potential harms, such as the generation of incidental findings
- The positive benefits associated with WES/WGS should be articulated in addition to the potential harms: the benefits might include increased scope of testing, to include a wider range of potentially causative variants: harms might include those associated with screening such as over-diagnosis, and the costs and burdens of future treatment.

### Operational Issues Group

The group considered its designated issues using the 100,000 Genomes Project as an exemplar, although some of the issues are also relevant to the provision of health services more generally. This project is being run by the Department of Health via a separate legal entity, Genomics England Limited, spanning clinical practice and research. The 100,000 Genomes Project plans to offer whole genome testing to individuals affected by rare diseases, cancer and infectious diseases. The following areas need to be addressed:

- Access: who will provide access to WGS to potentially eligible patients? On what basis will access be given, (e.g. that WGS is needed to make a diagnosis; that it will enable targeted treatment or care, patient based criteria or for other reasons, such as to inform reproductive choices or provide information to siblings or other relatives?) How can equity of access to WGS be facilitated? Looking to the medium and longer term, is it equitable to limit access to WGS to those who are already sick, or is there a role for health screening to be disseminated more widely?
- Analysis and reporting results: on what basis will sequence data be interrogated and reported back to a patient (through a protocol, or a list of genes that will be screened irrespective of phenotype or a tailored list)? What level of changes will be reported back (for example will single nucleotide polymorphisms (SNPs) be interrogated and reported or used as a basis for recruitment)? When testing children, the group recommended that where results for disorders other than those relevant to the child's presenting phenotype will be disclosed, that they should meet very high criteria for medical actionability.
- Consent: the process for securing consent should be meaningful, flexible and dynamic. Patients should understand the type of results that are likely to be generated and their implications. The balance between clinical and research use, should be explained, including the use of identifiable information, for example, through linkage of genotype and phenotype data as well as further sharing of identifiable or anonymised data. Research cohort studies could utilise an initial broad consent supplemented by participants opting in or out as the study progresses.

- Managing expectations: Patients may still have an expectation that, regardless of whether their samples and data are used for clinical care or research, there will be some clinical benefit. This may not be the case. Resources should be made available to follow up results generated through WGS/WES and appropriate additional investigation, treatment and screening provided. There will need to be prioritisation of resources and new pathways of care formulated. The extent to which patients (and participants of the 100,000 Genomes Project) will act on the results that are generated, will need to be evaluated.

These factors will need to be supported by an educated and informed workforce and patients, and facilitated by a regulatory environment that allows sharing of data with appropriate safeguards.

Focusing upon key areas of cancer, rare diseases and infectious diseases will facilitate access to genomic technologies within these specialties, but in the short term, participants are likely to be recruited to local centres of excellence. As well as ensuring equitable access to the technologies, in the longer term, as these technologies are implemented within health services, ongoing care, treatment and screening will also be important. Options for the 100,000 Genomes Project might be to hold the sequence data as a reference source, or to archive it or even discard inactionable results (although this compromises future flexibility). But as WGS/WES is rolled out in clinical care as a replacement technology for existing targeted genetic tests, using less targeted technologies such as WGS might allow a more structured approach which better matches presenting phenotype to genotype. This change in approach will need to be supported by education. In other countries it was suggested that the availability of the technologies would in itself create significant pressure to recruit patients and sequence their genomes despite the lack of evidence of clinical utility, and education and training is a way of mitigating this. Explicit guidance is needed about how to implement these technologies and the 100,000 Genomes Project can provide the opportunity to develop this process.

It seems feasible that there could be increased justifications for opportunistic screening using WGS technologies within some clinical specialties. This requires transparency about the motivations (*i.e.* whether screening is undertaken primarily for clinical or research purposes), particularly as research is not concerned with individual patient benefit. A dynamic consent model is needed which provides for broad consent for defined applications. More use could be made of electronic consents, providing for longitudinal access to data. However, in order for consent to be meaningful, patients and research participants need to understand which elements of their data will be used and for what purposes. Consent will also be needed to access phenotypic data. Managing expectations (hype v. hope) will be challenging.

Any results divulged to patients (whether pertinent or 'incidental') must meet very high criteria for seriousness and actionability. In a UK context, it would be unusual for the introduction of a new technology to change how to prioritise or fund a test. Thus if WGS/WES is likely to do this, there still needs to be mechanisms for determining access and ongoing treatment and follow-up.

# Issues that need to be addressed

A number of issues were raised repeatedly during the workshop. We suggest that a variety of policy approaches have developed across jurisdictions partly because these issues are not fully resolved.

In some instances, they could be resolved by further empirical research where the evidence base is sparse. In other instances, these issues are less tractable because other factors (such as variations in the infrastructure for delivering healthcare or reimbursement) are pre-eminent. Nevertheless, addressing these issues will help to ensure that policy is developed in a coherent manner. We suggest some action points in the concluding sections of this report.

## Question 1

*Is it ethically and legally acceptable to generate genomic sequence data on the basis that some of it will not be interpreted? To put this question another way, does generating raw genome sequence data from a patient (i.e. completing base calling and alignment) imply an ethical or legal duty to interpret the potential clinical significance of all of the sequenced data?*

Whole genome sequencing describes a process whereby short strands of DNA are analysed (primary analysis – base calling) mapped against a reference genome (secondary analysis - alignment) and then a filter applied, variants analysed and compared with databases of variation and interpreted (tertiary analysis - interpretation). There is a debate about whether it is legitimate for laboratory scientists and clinicians to hold sequence data but choose not to interpret it.

**YES:** In the United States, there is an increasingly prevalent view that physicians who order WGS for their patients are obliged to interpret the entire genome sequence. Old case law is supportive but not determinative<sup>3</sup>.

**NO:** Tertiary analysis of the genome sequence requires a deliberative step to use algorithms to interpret variants. Within a clinical setting, it is entirely legitimate for health care professionals to choose not to interpret certain known variants (for example, sequencing DNA in a child for variants which may predispose to late-onset diseases) provided that this decision is clear from the outset. This is the prevailing view in Europe. Moreover, in a publicly funded healthcare system, there should be no expectation that resources for sequencing, interpretation and on-going care will be made available.

<sup>3</sup> See the US law cases of *Pate v Threlkel* 640 S0 2d 183 (Fla Dist Ct App 1994) and *Safer v Pack* (1996) 677 A 2d 1188 (NJ Sup Ct, App Div).

## Question 2

*If data is interpreted, does this imply a duty to disclose this information to (a) the referring physician (b) the patient?*

**YES:** In the United States, there is concern that it is unacceptable for clinicians and laboratory scientists to hold interpreted sequence data without full disclosure to the patient. In privately funded health care systems in which the patient contracts with the clinician to provide health services, the medical notes and test records are owned by the funder (patient). If a patient were to bring a case against a clinician for non-disclosure of a genetic variant that could potentially be harmful, there may be a chance of a successful claim.

**NO:** The situation is less clear cut in Europe and the UK. Within a publicly funded health service, medical records and test results would probably be regarded as the property of the health provider rather than the patient. It might be less likely that a claim against a clinician or laboratory for non-disclosure of an incidental finding would be successful. Where variants are 'incidental' or 'unsolicited' and are not related to the presenting clinical phenotype, the potential benefits of disclosing these variants are less. This is because there is an ascertainment bias: within a clinical setting, the incidence and prevalence of particular genetic variants is calculated from that population of symptomatic (potential) gene carriers. The experience of these individuals may not be representative of the entire population of individuals who also carry those genetic variants, but who (have not yet) developed disease. This may be because they also carry other genetic or environmental variants that modify their risk in some way, or that not enough time has elapsed for the disease to become symptomatic. In short, better evidence is needed of the risks associated with particular genetic variants in individuals who are asymptomatic.

## Question 3

*Do clinicians have an active duty to search for other variants of diseases which are clinically actionable and serious and 'preventable'?*

**YES:** The development of genomic technologies such as WGS, and their increasing cost-effectiveness, potentially allows for a new paradigm within clinical medicine whereby clinicians can actively seek genetic variants which are clinically actionable, i.e. may enable the prevention of serious disease. Clinicians are justified in actively searching for other genetic variants in addition to the ones that are the subject of diagnostic inquiry for two reasons:

- The duty to do good (beneficence) is already established in medical care
- Since physicians owe an obligation to benefit their patients, it is justifiable to offer opportunistic screening for genetic variants, that are widely accepted to have serious, pathogenic effects, and that are clinically actionable, (meaning that there are opportunities to screen for or treat the diseases at an early stage which can benefit patients). Since the sequencing and interpretation of the entire genome will be done anyway for clinical reasons, this data will be generated in any event, and feeding back information about this 'incidental' information offers added value and a good use of resources.

**NO:** There is a lack of evidence that interpretation and disclosure of these additional variants is beneficial. This is partly because of the ascertainment bias mentioned above. It is unlikely that the variants detected using the technologies in this way, would satisfy the standards required of a national screening programme, with screening criteria being met, causing a lack of consistency in screening practice. Also, opportunistic screening of a subset of patients, within a health care system with finite funding, means that other health care resources may be denied or withdrawn from other patients. Offering opportunistic screening to only those patients who are already being investigated for other (unrelated) reasons is inequitable.

#### Question 4

*How far should patient choice guide the disclosure of clinical findings from WGS?*

##### 1 *Should the principle of autonomy or beneficence prevail?*

There was a vigorous debate about the contribution of the principles of autonomy (that individuals should be able to make decisions about their own lives), and beneficence (that wherever possible clinicians should maximise the benefit to their patients). Opinion was divided as to which ethical principle should trump the other when these principles conflict. Most delegates supported the view that patients or research participants should be offered some degree of choice about the results returned to them. This was felt most strongly when the results were incidental findings either in the sense of findings unrelated to the primary clinical or research objective, or findings from opportunistic screening performed as an adjunct to the primary activity (such as proposed by the ACMG, also called 'incidental findings'). However the mechanism for offering such choices remains unclear.

##### 2 *The potential for WGS to generate incidental findings.*

There was general agreement that as part of the consent process, patients should be made aware of the potential for WGS to generate incidental findings, and that 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. It should be made explicit that this practice supplements clinical care (or research). The majority also agreed that unless there is exceptional justification, access to clinical care (or research) should not be contingent upon agreeing to testing and return of a panel of additional variants.

##### 3 *Should patients decide what (class of) results are returned to them?*

There was discussion about whether it was desirable or feasible for patients to be offered choices about the type of genetic variants sequenced, interpreted and disclosed.

**4** *Are there ever situations in either clinical or research settings in which the patient's choice should be overruled?*

The circumstances in which a decision to oppose disclosure could be overruled are unclear.

**YES:** Some of the qualitative findings suggested that some stakeholders believed that it was sometimes justified for patient preferences to be overruled and for information about clinically actionable, serious variants to be disclosed against the wishes of competent adults. However, this tended to reflect unfamiliarity with the ethical principles which guide and resolve such disputes.

**NO:** If the consent process is to be meaningful, it should have addressed circumstances in which information might be disclosed without the explicit consent of the patient.

# Action points

The discussions at Workshop 1 generated a list of unresolved issues to be addressed in ongoing policy development. Together these suggest that much more multidisciplinary work needs to be done in a number of key areas:

**A. Explore the significance of the research/clinical boundary for genomics**

The ethical and legal principles governing the use of genomic technologies are related to the context of their use, and in particular, whether they are used within research or clinical care. Delegates felt that there needs to be more work to assess the impact of the research/clinical boundary for genomics technologies. This is a topic which we are taking forward in Workshop 2 of the Realising Genomics Project.

**B. Elucidate the pathway and step-wise processes that are needed for clinical genome sequencing and interpretation**

More clarity is needed about the judgements that are made as to the thresholds for base calling, alignment, variant calling and interpretation, as well as consideration of whether and how users may preferentially target interrogation and interpretation to specific areas of the genome. Much more investment needs to be put into the reference genomes and databases of variation that are used as comparators when constructing the patient genome, and assessing the significance of the variants within it. These databases need to be improved, so that they are more reliable and comprehensive. The various databases also need to be rationalised and streamlined. Precise details of the actions that are needed will depend upon how sequencing technologies are likely to be rolled out into clinical practice.

**C. Clarify how the implementation of WES/WGS is likely to impact upon existing processes for consent and disclosure**

Two issues that emerged strongly from the meeting was the need for clarity and transparency. These need to be reflected in the content and the processes for taking consent and for disclosure. We will explore these in more detail in Workshop 3.

**D. Explore alternative strategies for taking consent and disclosure**

The presentations from Workshop 1 emphasised the need for processes to be put in place to address possible differences in perspective between health care professionals and their patients. In order to address this, dispute resolution strategies such as explicitly warning of the possibility of enforced disclosure at the outset, using an independent committee to arbitrate where outcomes are contested, and increased provision for dynamic consent need further exploration, and again, this is something that will be taken forward in Workshop 3.

# Appendix 1 Workshop 1 delegate list

| Delegate                 | Title                                                                                                                                |
|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| Ms Corinna Alberg        | Project Manager, PHG Foundation, Cambridge                                                                                           |
| Dr Barbara Biesecker     | Associate Investigator, National Human Genome Research Institute/NIH, Bethesda, Maryland, USA                                        |
| Dr Leslie Biesecker      | Chief Investigator, Genetic Disease Research Branch, National Human Genome Research Institute/NIH, Bethesda, Maryland, USA           |
| Ms Gill Crawford         | Clinical Doctoral Fellow, CELS (Clinical Ethics and Law at Southampton), University of Southampton, Southampton                      |
| Ms Alison Hall           | Programme Lead (Humanities), PHG Foundation, Cambridge                                                                               |
| Dr Nina Hallowell        | Associate, PHG Foundation, Cambridge                                                                                                 |
| Dr Ari Haukkala          | University Lecturer, Department of Social Psychology, University of Helsinki, Finland                                                |
| Dr Lidewij Henneman      | Associate Professor, Senior Researcher, Department of Clinical Genetics, Community Genetics, VU University Medical Center, Amsterdam |
| Mr Leigh Jackson         | Researcher, University of Plymouth, Plymouth                                                                                         |
| Dr Jane Kaye             | Director, HeLEX, Department of Public Health, University of Oxford, Oxford                                                           |
| Dr Mark Kroese           | Programme Director, PHG Foundation, Cambridge                                                                                        |
| Dr Leila Luheshi         | Programme Lead (Life Sciences), PHG Foundation, Cambridge                                                                            |
| Dr Anna Middleton        | Ethics Researcher & Registered Genetic Counsellor, The Wellcome Trust Sanger Institute, Genome Campus, Hinxton, Cambridge            |
| Dr Fiona Miller          | Associate Professor, Institute of Health Policy, Management & Evaluation, University of Toronto, Ontario, Canada                     |
| Professor Michael Parker | Professor of Bioethics and Director of the Ethox Centre, Nuffield Department of Population Health, University of Oxford, Oxford      |
| Dr Joanne Whittaker      | Senior Fellow, PHG Foundation, Cambridge                                                                                             |
| Dr Ron Zimmern           | Chairman, PHG Foundation, Cambridge                                                                                                  |

# Appendix 2 Programme

| Day 1 |                                                                                                                                                                                |                                |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| 10.00 | Arrivals                                                                                                                                                                       | Coffee on arrival              |
| 10.30 | Introduction                                                                                                                                                                   | Mark Kroese and Alison Hall    |
| 11.00 | Hypothesis-generating research and predictive medicine                                                                                                                         | Les Biesecker                  |
| 11.40 | Informed consent for exome sequencing in diagnostics: patients' and professionals' experiences                                                                                 | Lidewij Henneman               |
| 12.20 | Developing management pathways for the return of clinically significant findings                                                                                               | Jane Kaye                      |
| 1.00  | LUNCH                                                                                                                                                                          |                                |
| 2.00  | Genomic Tests: health care professional and family experiences of managing incidental information                                                                              | Gill Crawford                  |
| 2.40  | Genetic incidental findings in research and the clinic                                                                                                                         | Leigh Jackson                  |
| 3.20  | International attitudes towards sharing 'incidental' findings from whole genome research studies: empirical data from health professionals, genomic researchers and the public | Anna Middleton                 |
| 4.00  | Break                                                                                                                                                                          |                                |
| 4.30  | Preferences for return of sequencing results among ClinSeq participants and parents of children with undiagnosed conditions; and perceptions of uncertainty                    | Barbara Biesecker              |
| 5.10  | What is a meaningful result? The challenges of clinical sequencing                                                                                                             | Fiona Miller                   |
| 5.50  | Ways of thinking about ethics when 'realising' genomics at the clinical-research interface                                                                                     | Mike Parker                    |
| 6.30  | Wrap up                                                                                                                                                                        | Alison Hall and Nina Hallowell |
| Day 2 |                                                                                                                                                                                |                                |
| 9.30  | Start and introduction to day 2                                                                                                                                                | Nina Hallowell                 |
| 9.45  | Identifying of key themes from day 1                                                                                                                                           |                                |
| 11.00 | Coffee                                                                                                                                                                         |                                |
| 11.20 | Implications for practice of a theme                                                                                                                                           | Small group work               |
| 1.15  | LUNCH                                                                                                                                                                          |                                |
| 2.00  | Feedback from small groups                                                                                                                                                     |                                |
| 3.00  | Key issues that need resolving and require policy – implications for research/clinical interface and patent pathway                                                            |                                |
| 4.00  | Closing remarks                                                                                                                                                                | Ron Zimmern                    |

# Appendix 3 Professional guidance on the return of incidental or unexpected findings

1. There is an 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<sup>4</sup>.
2. The PHG Foundation published a discussion paper exploring the ethical and legal basis for the disclosure of incidental findings arising from clinical care and research in April 2013. The UK Government has initiated the 100,000 Genomes Project (100KGP) to sequence 100,000 whole genomes of NHS patients affected by rare diseases, cancer and infectious diseases. Using this project as an exemplar, the paper explores how the setting (i.e. research or clinical care) impacts upon the management of pertinent and incidental findings. It discusses the ethical and legal duties of researchers and clinicians and suggests a framework for disclosure and some recommendations for best practice. In particular it recommends that - a) research and clinical activities should be clearly distinguished within the 100KGP; b) explicit informed consent for the disclosure of pertinent and incidental findings generated from research studies performed as part of the 100KGP should be sought; c) that only research findings that are scientifically and clinically significant and severely or moderately life-threatening and clinically actionable be disclosed as part of the 100KGP; and d) that participants in the 100KGP be permitted to opt out of disclosure if they so wish. We suggest that many of these recommendations - concerning the primacy of consent and the principles of disclosure - are generalisable to the future implementation of WGS/WES in clinical settings.
3. The PHGF discussion paper was published in advance of two key sets of recommendations from professional groups in USA and in Europe. The American body, 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,

<sup>4</sup> 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](http://www.acmg.net/docs/ACMG_Releases_Highly-Anticipated_Recommendations_on_Incidental_Findings_in_Clinical_Exome_and_Genome_Sequencing.pdf)

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.

4. The ACMG have published an additional clarification<sup>5</sup>. 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.'
5. 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 children<sup>6</sup>, and genetic testing more broadly<sup>7</sup>. 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), 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 healthcare professional should report such genetic variants.'
6. 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, re-contact and the interface between clinical and research settings. Thus their approach is more consensual, building on existing policies and practice.

<sup>5</sup> American College of Medical Genetics and Genomics (2013) ACMG [http://www.acmg.net/docs/Incidental\\_Findings\\_in\\_Clinical\\_Genomics\\_A\\_Clarification.pdf](http://www.acmg.net/docs/Incidental_Findings_in_Clinical_Genomics_A_Clarification.pdf)

<sup>6</sup> 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](http://www.ethox.org.uk/Documents%20and%20images/GTOC_2010_BSHG.pdf) (accessed 11.6.13)

<sup>7</sup> 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

# Appendix 4 Definition of incidental findings: the prerequisite scientific and clinical validation

In our view, 'incidental findings' are those findings that have two defining characteristics<sup>8</sup>:

- 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.

<sup>8</sup> PHG Foundation (2013) Managing incidental and pertinent findings from WGS in the 100,000 Genomes Project: A discussion paper from the PHG Foundation. Accessed at <http://www.phgfoundation.org/news/13721/> on 31.10.13

## About the PHG Foundation

The PHG Foundation is a pioneering independent think-tank with a special focus on genomics and other emerging health technologies that can provide more accurate and effective personalised medicine. Our mission is to make science work for health. Established in 1997 as the founding UK centre for public health genomics, we are now an acknowledged world leader in the effective and responsible translation and application of genomic technologies for health.

We create robust policy solutions to problems and barriers relating to implementation of science in health services, and provide knowledge, evidence and ideas to stimulate and direct well-informed discussion and debate on the potential and pitfalls of key biomedical developments, and to inform and educate stakeholders. 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  
+44 (0) 1223 761 900

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