

ELSI* and the implementation of WGS / WES in clinical practice

The Realising Genomics Project is a PHG Foundation initiative which, through four stakeholder workshops, will generate new conceptual and policy thinking to support the clinical implementation of whole genome sequencing (WGS) and whole exome sequencing (WES), increasing the potential for these novel genomic technologies to improve patient care within the UK NHS.

*Ethical, legal and social issues

At the first workshop, invited international researchers, bioethicists, social scientists and lawyers discussed the key challenges and outstanding questions for future policy development to support the ethical, legal and socially responsible implementation of genomic medicine.

Topics covered in the discussion included:

- The implications of the use of genomic technologies in a research setting for clinical implementation
- Ethnographic and qualitative studies of existing clinical genetics practice to identify the challenges that might be presented by introducing whole genome testing
- The strategies currently used by clinicians to manage uncertain, unexpected or incidental findings in clinical genetics
- Research on consent procedures for the return of genomic test results
- Attitudes and expectations of key stakeholders, including health care professionals and patients/

participants to genomic technologies, including WGS

- Attitudes of health professionals, patients, ethics committees, researchers and families about the return of incidental findings and managing the return of clinically significant findings from research.

Key observations:

- 1 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 still evolving.
- 2 The setting - research or clinical - where testing occurs, influences the ethical principles that apply, although the boundary between these activities is becoming increasingly blurred.

For more information about the Realising Genomics project or a copy of the report from Workshop 1 contact Alison Hall at:

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Policy challenges to socially and ethically responsible implementation of genomic medicine

Delegates proposed and ranked a set of the main ethical, legal or social issues/challenges raised by the implementation of WGS technologies into clinical care:

Datasets

The large datasets of genetic variants generated by these technologies will need interpretation if they are to be used within the clinic. Managing and understanding the complexity of data, mechanisms and treatment will be a challenge, particularly in rare diseases. Bioinformatics pipelines need to be developed and managed to allow meaningful data feedback to clinicians with the ultimate aim of guiding clinical interventions. These bioinformatics pipelines must 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 resequencing.

Trust, consent and expectation management

Successful introduction of genomic medicine into the NHS will depend on the development of meaningful consent processes that protect patient autonomy whilst also not undermining the professional's ability to discharge their duty of care. For example, reports from the workshop suggested 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. In order to maintain trust in the consent process, and in the patient-clinician relationship more widely, 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.

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.

Evaluate the clinical-research interface

Evidence from the workshop suggested that the boundary between research and clinical practice is losing its current distinction through 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 the second workshop, 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.

Provide education and training to enable patients and practitioners to work together to make informed decisions

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 introduction 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.

Acknowledge the tension between resource limitations and equity of access to genomic tests

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. Robust and objective criteria for commissioning these technologies should be developed prior to their adoption by health services.

Clarify the risks and benefits associated with using genomic tests for opportunistic screening in the absence of disease/symptoms/phenotype

The comprehensive nature of WGS/WES enables the investigation of a genome for the presence of variants that are unrelated to the individual's 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. 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.

Establish a consensus about when it is appropriate to offer genomic testing to children

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 a child to make autonomous decisions for him or herself in the future, as against the need to act in the child's current best interest.

Cross-cutting issues

The requirement for conceptual clarity was identified as an overarching issue. A failure to distinguish between 'pertinent' and 'incidental' findings, between 'testing' and 'screening' and existing medical problems, genetic predisposition and benign traits exacerbates policy differences. These could be partially resolved by 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:

1. **Scale**
How are genomic technologies likely to be implemented within clinical settings? How will they be translated from research to clinical settings?
2. **The requirement for conceptual clarity**
What is current practice within research and clinical arenas? Are there areas of practice and proposed implementation that require greater clarity and transparency?
3. **Operational issues**
What operational issues are likely to be important when implementing WGS/WES for clinical purposes?

Outstanding questions

- Is it ethically and legally acceptable to generate genomic sequence data on the basis that some of it will not be interpreted? Does generating raw genome sequence data from a patient (*i.e.* completing alignment and base calling) imply an ethical or legal duty to interpret the potential clinical significance of all of the sequenced data?
- If a clinician or scientist interprets the clinical significance of identifiable genomic data, does this imply a duty to disclose this information to (a) the referring physician (b) the patient?
- Do clinicians have a duty to search purposefully in whole genome/exome data to identify variants associated with risk of serious diseases unrelated to the presenting complaint, which are actionable or preventable?
- How far should patient choice guide the disclosure of clinical findings from WGS? Should patients decide what class of results are returned to them? Are there ever situations in either clinical or research settings in which the patient's choice should be overruled?

We will be addressing these questions with invited stakeholders at three further workshops. The final report will be published in autumn 2014.

The PHG Foundation is an independent think-tank, uniquely focused on the application of genomics and other emerging health technologies for more accurate and effective personalised medicine.

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