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Genomics and the boundary between research and clinical care and treatment

The *Realising Genomics* project is a PHG Foundation initiative to generate new conceptual and policy guidance to support the clinical implementation of whole genome sequencing (WGS) and whole exome sequencing (WES) in the UK NHS. This note describes the discussions and outcomes from a workshop: *Realising Genomics in clinical practice: the research clinical interface* - the second of four multidisciplinary workshops held as part of this project.

Introduction

The distinction between clinical care and research is clear from a regulatory perspective: different ethical and legal principles apply, but there is concern that technological developments in genomics are moving at such a rapid pace that this boundary is becoming increasingly blurred and that it is often difficult for patients to distinguish these activities. The purpose of the workshop was to explore this interface from the perspective of a variety of stakeholder groups and consider how it impacts on the implementation of these technologies.

The clinical perspective

The primary concern of clinicians is to provide care for their patients. Sometimes this involves accessing interventions that are only available in research settings. Whilst clinicians generally are clear about the differences between clinical care and research, there are a number of reasons why this boundary sometimes appears blurred:

- Some novel diagnostic tests or treatments are only accessible in a research setting. Clinicians may enable their patients to access these tests to facilitate a diagnosis.
- Patients may see their care as being seamless and the distinction between clinical care and research may lack significance for them, particularly if their clinician is also involved in the research.
- Research such as the Deciphering Developmental Disorders (DDD) project systematically recruits NHS patients for further investigation, including WES, where existing clinical investigation has failed to yield a diagnosis.

Technological developments in genomics are moving at such a rapid rate that the boundary between clinical care and research is becoming increasingly blurred and it is often difficult for patients to distinguish these activities

The legal obligations arising in clinical care and research are not always easy to characterise

- In recent years there has also been a more deliberate and systematic integration of research into clinical practice through NIHR, academic health science networks and other initiatives.
- Whilst empirical work on clinicians' attitudes suggests that many clinicians use research pragmatically to obtain a diagnosis for their patients and/or access novel treatments, clinicians nevertheless recognise that the two settings drive different legal obligations and utilise different standards of evidence in order to support these interventions.

The legal perspective

The legal obligations arising in clinical care and research are not always easy to characterise. Some questions relate to the data that is generated: who has access to this data for what purposes? Other elements concern rights of disclosure (for example to be warned of a genetic risk). These rights should be balanced against 'the right not to know'. In a genomics context, the extent of sharing data with family members is also an important issue.

The law in the UK is complex, comprising common law duties (such as confidentiality); statute (such as the Data Protection Act 1998 and Human Rights Act 1998); and softer law (including the Council of Europe Convention on Human Rights and Biomedicine, associated Protocols and professional guidance). Two distinct types of claims are relevant when considering obligations arising from information management: those which protect individual autonomy, which tend to be seen as absolutist, and privacy claims, which are not regarded as such.

The workshop discussed the scope of the duty and standard of care arising in research and in clinical care, and the impact that introducing WGS and WES might have. In the absence of determinative legal cases, a British court might question whether revising the standard of care to take account of WGS / WES is fair, just and reasonable. A court might also consider how the context of research or clinical care might require or prohibit certain behaviours with the information that is generated.

The ethical perspective

There are good reasons for applying different ethical frameworks to research and clinical care: the motivations for each are different, where harms result they are different, and a clear distinction between the two minimises the therapeutic misconception (*i.e.* the misguided assumption that the researcher is necessarily acting in the best interests of an individual patient).

Clinical ethics has adopted a patient-centred approach where the patient's best interests frame the debate. In a research setting, the principles of autonomy and that of imposing a minimal risk together frame the ethical approach. Research ethics also takes account of the wider interests of society, such as the generation of new knowledge, rather than individual interests.

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Small group discussion

How clear is the interface between research and clinical care in genomics?

There was a clear consensus amongst workshop delegates that research and clinical practice are viewed and pursued as separate activities by clinicians. However, these activities are inter-dependent at times, making the boundary between them sometimes permeable and ambiguous. This distinction was felt to be less clear to patients who sometimes regard research activities as an extension of their clinical care.

What impact does the use of WGS and WES have on this interface?

The impact of the implementation of WGS and WES both in clinical genetics services and more widely, will depend on how and where they are used. Thus relevant questions concern the extent to which sequencing, annotation and interpretation are targeted differently for clinical or research contexts. Research may require a lower degree of clinical utility and analytical validity; thus results generated in a research setting that are applied for clinical use will need to be validated and verified. Many delegates had reservations about applying lower thresholds of utility and the potential destabilisation of existing clinical service provision. Delegates also noted that the scale of the results likely to be generated, the absence of a robust evidence base and the lack of resources to fund resultant patient care create serious concerns that patients may not be adequately supported through this process.

Would the introduction of a hybrid model be necessary or desirable?

There was support for a model of practice that enabled both clinical care and research to be done in parallel, but not for a distinct category or hybrid activity in which clinical and research elements were indistinguishable from an ethical and regulatory perspective.

Key challenges for implementation of WES/WGS in clinical care

1. Lack of transparency about whether the activity is research or clinical care

Recommendation: The distinction between clinical care and research should be made more explicit in communications with patients including in information sheets and consent forms across clinical specialties. This is particularly important where clinicians also recruit their patients for research.

2. Genomic research using these technologies potentially involves activities that until recently have been confined to clinical settings (e.g. to validate potentially clinically relevant findings, refer for further investigation or disclose research findings, including unexpected results).

Recommendation: The obligations of researchers using these technologies need to be clarified, particularly if this involves re-contact or ongoing follow-up. The thresholds for reporting findings need to be made explicit. Consent processes should clarify whether such findings will be reported once clinically valid evidence criteria are met, who will initiate this and over what timescale. Delegates noted that an improved evidence base is urgently needed to assist in sequencing, annotation and interpretation.

Delegates had reservations about results generated in a research setting being applied for clinical use without sufficient validation and verification

3. **More systematic enrolment into research using these technologies will lead to increasing numbers of patients/research participants who may have expectations that clinically relevant information will be provided to them.**

Recommendation: If clinically valid findings are to be fed back, additional resources are required both to validate findings to a clinical standard, and to provide appropriate clinical support. More empirical evidence is needed to ensure that this approach has clinical utility and that it does not harm patients.

4. **There is a lack of clarity about the parameters of data protection, both as to the type of data which is protected (such as 'de-identified' genomic data) and the nature of those protections (for example, whether rights extend to family members of the data subject).**

Recommendation: There needs to be a better understanding of how this type of information might be shared within families, and how this can be reconciled with a regulatory regime that prioritises individual rights.

5. **Draft European regulation currently under review (April 2014) creates additional uncertainty about the lawfulness of data sharing especially for research in several key areas: the requirement for consent to be specific, explicit and informed; sharing for secondary research; and the breadth of any 'public interest' exemption.**

Recommendation: In the UK, the Government has ratified the Information Governance Review's recommendation for effective regulation to ensure the safe, effective, appropriate and legal sharing of personal confidential data in a balanced and proportional manner. Potential friction between UK and European law needs to be addressed and resolved, particularly how the cumulative requirements for consent can be met. In this transitional period, communications with patients need to be explicit about the rate at which research findings are being generated and that evidence and practice are likely to change rapidly as a result.

We will be addressing these issues with invited stakeholders at further workshops in the *Realising Genomics* project series. The final report will be published in autumn 2014.

The PHG Foundation is an independent health policy think-tank based in Cambridge, UK. Our mission is making science work for health.

To learn more about this project, see:
www.phgfoundation.org/project/realising-genomics

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