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# Genomic sequencing technologies and patient pathways

Whole genome sequencing (WGS) and whole exome sequencing (WES) are transformative technologies, but their effect on patient pathways within publicly funded health systems needs clarification. This briefing note describes key findings from an international multidisciplinary workshop, which concluded that the extent of interpretation of genome sequence is a key determinant of the ethical, legal and social issues (ELSI) that may arise.

WES / WGS services are being implemented, and the impetus to adopt them will increase once they are able to offer genuine cost savings over existing technologies across the entire patient pathway.

## Introduction

Single gene tests have limited clinical utility in conditions which have multiple genetic causes (heterogenous conditions), and gene panel tests utilising next generation sequencing technologies (NGS) are increasingly used to enable parallel testing of multiple genes implicated in particular phenotypes. This approach has improved diagnostic yield compared with diagnostic strategies using conventional technologies such as Sanger testing. However not all available tests are commissioned and NHS access to clinically appropriate genetic tests remains variable for patients and their families.

## Whole exome sequencing in clinical settings

Various groups have extended the scope of sequencing and interrogation across the whole exome and this technology is becoming available within some clinical settings. Like NGS gene panel testing, exome sequencing typically utilises a standardised workflow, enabling greater automation and throughput at reduced cost compared to non NGS tests. Amending a pipeline to add additional genes incurs some costs but enables sequence data to be re-interrogated bioinformatically although ongoing data analysis and interpretation remain costly and time-consuming.

## Opening the exome

An open exome approach improves diagnostic yield in patients with severe intellectual disabilities. However, open genome approaches have a higher likelihood of generating inconclusive results, including more incidental findings (unrelated to the presenting phenotype, but not necessarily clinically actionable).

### 'Gene package' approach

An approach developed in Radboud UMC, Nijmegen, Netherlands offers targeted interpretation of the exome sequence guided by:

1. Gene packages incorporating only known pathogenic genes for the phenotype under review (including severe intellectual disability, blindness and movement disorders).<sup>1,2</sup>
2. The comparison of sequences from the proband and their parents to identify novel disease causing mutations.<sup>2</sup>

If targeted approaches are inconclusive, the Nijmegen group 'open' the exome sequence for re-analysis (see panel, left).

### The UK context

Genetic testing for rare diseases is usually accessed through clinical genetics teams which uses a systematic pathway incorporating consent, test provision, interpretation, and reporting. The workshop explored how a phased approach (*i.e.* gene package followed by open sequencing) might change patient pathways in the UK. The key difference is that an open exome approach involves sequencing the whole exome of 21,000 genes prior to interpreting a small proportion guided by the patient's phenotype. Regardless of whether filtering is used before sequencing (*e.g.* gene panels) or after (*e.g.* exome testing), interpreting variants as pathological or not is complex, with objective and subjective elements causing variability in the results generated and reported. However, WES / WGS is cost-effective where there are multiple genes and variants that could be causing the patient's disease, and therefore uncertainty about the role of particular variants. Additional variability occurs because laboratories differ in the evidence they use to evaluate findings: most combine in-house specialist databases with publicly available databases, and data sharing between laboratories is not routine.

### Operational impacts

The workshop analysed how existing patient pathways might change with WES and WGS, considering (1) the process of consent; (2) technical aspects (3) the disclosure of results to patients. The conclusion was that the most important distinction in terms of ELSI, is the extent to which the interpretation of the genome sequence is open or filtered.

### Impact on the consent process

In the short term, most WES / WGS technologies will be accessed via clinical genetics services or via community paediatricians/neurologists but with referral to clinical genetics if a positive result is obtained. The consent process should cover the reliability of the test, the consequences of not proceeding as well as the broad risks and benefits of going ahead, focusing on the general nature of the diagnostic test, the potential for generating and disclosing any incidental findings and the possibility of re-contact. A pragmatic approach might be to simultaneously seek consent from patients for various elements: targeted and open approaches and subsequent re-contact.

## Implications for technical aspects of sequencing and interpretation

The criteria for including genes for analysis should follow existing specifications (*i.e.* peer reviewed published data involving more than one source supported by functional and segregation evidence). The analysis pipeline and validation should not be prescribed, but coverage, read depth and gaps should be reported. The most problematic results are those of uncertain pathogenicity: interpretation of these will be the key bottleneck and needs to be better resourced. The evidence base used for filtering (*i.e.* for selecting gene/variant inclusion for exome analysis) and interpretation is variable and incomplete. Using standardised vocabulary and ontology such as the Human Phenotype Ontology would enable greater automation.<sup>3</sup>

More data sharing is needed. By collating multiple unrelated cases with sufficiently similar phenotypes it will be possible to improve data quality, supplement phenotypic information and facilitate more systematic evaluation and decision making in filtering and interpretation. Inadequate infrastructure and unwillingness are hampering data sharing: these might be resolved by creating a unified database and sharing infrastructure and making funding for laboratory services contingent upon data deposition.

## Implications for disclosure to clinicians and to patients

Patient pathways will need to be adapted as referrals routes widen to include non-genetic professionals. Accurate and full phenotype and family history should guide the variants that are interpreted, supported by electronic data collection systems. Reports must suit the context and expertise of the referrer and specify where additional clinical genetics involvement is needed.

Feedback to patients should be step-wise, prioritising clinically relevant information. Approaches to re-contact or re-analysis of inconclusive results vary: patients typically want relevant information especially if actionable, but most delegates felt that re-contact should be limited to an episode of care. Delegates rejected the argument that generating clinically actionable incidental findings would, in itself, create an obligation to disclose these to patients.

## Translational challenges

### 1. Changes to the patient pathway

Changes to the patient pathway are likely to be modest if NGS technologies are implemented in a targeted manner. For a minority of clinical applications, broader NGS approaches will necessitate more substantial changes.

### 2. Use of WGS/WES as first line test

The clinical utility associated with utilising WGS / WES as a first line test in specific clinical scenarios remains to be established.

### 3. Filtering/targeting

Advantages of using a 'gene package' approach are easier implementation and generating fewer variants of unknown significance and incidental findings, thus minimising potential ethical, legal and social challenges that might arise.

## Factors vital to effective use of WES/WGS in clinical practice:

- Collection of phenotype data and its use to guide testing and data interpretation
- Improved data sharing practices between laboratories to help to populate the evidence base to be used to interrogate variants of known and unknown significance
- Development of alternative bioinformatic packages for use with for a range of clinically determined applications.

If laboratories fail to share these databases, this may lead to service failures as centres diversify to offer genomic analysis in genes in which they have little prior experience.

**4. Phenotypic characterisation**

More work needs to be done to enable the systematic and iterative collection of phenotypic information to inform genomic analysis and interpretation. This may require major systematic investment in design and development of infrastructure and processes.

**5. Interpretation**

Processes must be put in place to formalise and harmonise the interpretation and reporting back of variants that are either (i) of unknown significance or are (ii) serious incidental findings that are potentially clinically actionable. The use of expert committees should be explored.

**6. Emerging standards**

Services within the NHS need to develop evidence based consistent harmonised laboratory and clinical standards in order to ensure equitable service provision and acceptable quality assurance across the entire NHS.

**7. Validation**

As WGS / WES services mature, the requirement for validation using an alternative technology (such as Sanger sequencing) for quality assurance purposes seems likely to diminish.

**8. Consent**

The consent process for clinical sequencing involving gene packages and open sequencing requires further development.

**9. Disclosure**

More empirical work is needed to understand the potential impact of disclosure of findings arising from WGS / WES.

**10. Recontact/reanalysis**

There was support for systematic re-analysis and re-contact but significant concerns that the associated cost and workload would be prohibitively high. More work is needed to determine how to operationalise this whilst addressing the ELSI issues that might arise.

**11. Combined models for service provision and funding (private/public partnerships)**

Sequencing and interpretation services seem likely to be secured through a mix of private and public providers. International efforts to agree minimum standards for diagnostic pathways are vital.

**References**

1. Neveling K *et al.* (2013) *Human Mutation* 34;12:1721-1726.
2. De Ligt J *et al.* (2012) *N Engl J Med* 367;20: 1921-1929.
3. Robinson P *et al* (2008) *AJHG* 83;5:610-615.

Find out more about the *Realising Genomics* project on our website.

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