Guidelines for diagnostic next generation sequencing

The PHG Foundation welcomes the publication of Eurogentest’s guidelines for diagnostic next generation sequencing, which are timely, comprehensive and a very useful addition to existing guidance.

In particular, we welcome the suggestion that there is transparency about the extent of quality and comprehensiveness of different NGS assays, and using a common rating system would be a good way of achieving this. The Eurogentest guidelines also highlight the increasingly blurred boundaries between research and clinical care. Transparency about the setting and the objectives of testing is important: the guidelines are also useful in highlighting the circumstances where these activities might overlap.

Diagnostic next generation sequencing technologies are on the cusp of implementation in clinical settings, and many of the topics and issues considered in these guidelines are also addressed in a recent report from the PHG Foundation ‘Realising Genomics in Clinical Practice’. The remit of this project was to identify the broad range of ethical, legal, social and practical issues that will arise from the use of expanded NGS gene panels using selected gene lists through to genome-wide sequencing technologies within a clinical setting. Building on background research and analysis over a two year period, this project consisted of five iterative workshops culminating in a comprehensive set of recommendations for implementing these technologies in ways that improve health care while minimising potential harms.

In many respects, there are common themes between the recommendations in the Eurogentest’s guidelines, and the recommendations in the *Realising Genomics* report (RG):

- The use of core disease gene lists is encouraged on the basis of providing consistent test provision
• It is recognised that data sharing is key in providing the evidence base through which variants of unknown significance can be better interpreted, thus providing a safer and more effective diagnostic service for patients

However, there are some differences in approach which we would specifically like to highlight. These are areas that might require sustained policy development and greater discussion, as the technologies become embedded into clinical services across Europe.

**Reanalysis and recontact**

The Eurogentest approach to reanalysis and recontact is different from that in the *Realising Genomics* report. Eurogentest use the contractual relationship between the laboratory and the clinician as the basis for analysing the responsibilities to the patient regarding reanalysis. Our approach was to use the best interests of the patient, as a starting point. Our considered view (following evaluation and discussions with stakeholders) was that reanalysis was sometimes justified, whether it originated from the clinician, the laboratory or even the patient. If reanalysis is to be carried out, these factors are relevant:

• The possibility of reanalysis (and recontact) should be explicitly addressed as part of the consent process ([RG recommendation 10](#)). This is important to ensure that patients are able to make autonomous and informed choices about their care

• A systemic, evidence based approach should be taken to reanalysis and recontact. Standardised approaches should be developed through professional standards and guidelines ([RG recommendation 18](#)). This is important to ensure that there are consistent approaches between providers, and that ‘ad hoc’ approaches do not favour some patients (or patient groups) over others

• Reanalysis should usually be triggered by the original referring clinician (but this might be in response to an enquiry from a patient, or alert received from the laboratory)

• Ongoing research on ethical, legal and social issues and on health economics is needed to inform the merits and potential harms of reanalysis and recontact.

We therefore believe that there may be circumstances where the systematic reanalysis of ‘old’ or existing data may be justified on a number of grounds, particularly where whole genome or exome sequence data has been stored, and the cost of repeating sequencing in response to a new request from a
The Eurogentest approach to reanalysis and recontact is different from that in our *Realising Genomics* report, in which we take as a starting point the patient’s best interest.

The Eurogentest approach to reanalysis and recontact would be prohibitve. In the UK, the route for reanalysis and recontact would be via the referring clinician, so unlike the Eurogentest guidelines (at paragraph 5.05 page 47) we think it is unlikely that the laboratory would recontact patients directly. The laboratory would have responsibility for alerting the referring clinician that there are grounds for patient data to be re-examined.

If there is no prospect of reanalysis, the timing of the test will become an explicit determinant of test outcome: there would need to be concerted efforts to ensure that current undiagnosed patients receive the same quality of care as ‘future’ patients.

We therefore suggest that statement 5.05 should be revised to allow for reanalysis if clinically justified (and to make it less categorical that systematic reanalysis should not be done).

**Gene lists**

The Eurogentest guidelines include a recommendation that core gene panels be developed by multidisciplinary groups, which we welcome. However, it is not clear how consistent these lists are required to be, between different providers as Statement 2.04 simply stipulates that ‘core disease gene lists’ should be established by clinical and laboratory experts. In the *Realising Genomics* Project, we made an explicit recommendation that the NHS should adopt targeted analysis using gene lists following genome-based sequencing as an assay ([RG recommendation 1](#)). Phenotype should guide the use of these gene lists ([RG recommendation 3](#)) and standardised evidence criteria should be developed for the selection and evaluation of genes in gene lists. We envisaged that this would be done by a national multidisciplinary committee. Secondly, we recommended that once these criteria are agreed, mechanisms be developed for the relevant experts in each specified clinical area to identify core gene lists for specific phenotypes relevant for their specialty: each gene list should be developed, curated and updated by a multidisciplinary expert group comprising representative and relevant experts (including health care professionals and NHS scientists). This could potentially build on the committees that are to be established as part of the 100,000 Genomes Project.

**Classifications of core lists**

It might work well to have different classifications of core gene lists (as per statement 2.03 page 16) – those that require additional Sanger sequencing to fill gaps post NGS and those that are sufficiently covered without fill-in. This approach would be transparent, consistent between providers, yet pragmatic.

If this approach were to be developed within and between European member states, we suggest the following:
• That there should be transparency about which genes are included so that gene lists can be compared

• That there could be provision for European MDT meetings between providers of core panels for the same disorder, to compare the genes that are included and excluded

Data sharing

We strongly support the stance taken in the guidelines in support of data sharing and variant interpretation, namely that diagnostically relevant data be collected in national or international databases (p. 46). Although there is some elaboration on pages 51-52, we think it would be helpful if the guidelines could give some examples of suitable databases for deposition and clarify explicitly the extent to which this statement applies to unknown variants or variants of unknown significance. In the *Realising Genomics* report, we recommended that laboratories be mandated to deposit variant data (including relevant clinical data) into a secure, comprehensive, accessible database (*RG recommendation 12*).

Data disclosure and feedback of findings

Statement 3.01 includes a list of items which the laboratory should provide for each NGS test. Presumably these are all reportable to the referring clinician. Statement 5.01 identifies a set of key facts that should be contained in a summary report ‘on one page’ (which may be an ambitious target). We agree that these facts should be readily accessible to the referring clinician. This is particularly true if the test is commissioned by a non-clinical genetics professional, as NGS diagnostic tests are mainstreamed into other clinical specialties. Our report emphasised the support that might be needed to ensure that all users extract maximum value from testing (including understanding the components of appropriate referral, consent processes, and interpretation). Laboratory staff will often play an invaluable part in this process.

The management of secondary/unsolicited/incidental findings is a pressing challenge, especially when considering the optimal implementation of whole exome and whole genome sequencing (as in the *Realising Genomics* report). However the two approaches are quite similar in that they take as their starting point the need to minimise the generation (and subsequent analysis and interpretation) of non-pertinent findings. To the extent that incidental or secondary findings are generated - in the *Realising Genomics* project, we concluded that patients should be given the opportunity to express their views in advance as to whether IFs generated from genomic sequencing should be disclosed to them. Reporting separately on secondary findings (as suggested on page 23, paragraph 3.2.2) would be one way of managing this process.
Consent for whole exome or whole genome sequencing

On page 24, it is recommended that separate counselling be done before whole exome or genome sequencing. In the Realising Genomics project we recommended that a separate counselling session should not be mandated, but should be left to the clinical judgement and expertise of the clinician, taking into account their knowledge of the patient. This reflected widely differing views on this issue amongst the various stakeholder groups who were consulted (RG report pages 31-32).

Rating scale

The introduction of a rating scale would enable greater comparison between tests by laboratories and clinicians, and would help users to assess test reliability, as well as achieve a more equitable service for patients. However, there may be some instances where achieving an A rating would not result in additional clinical utility (as per the discussions about core gene lists of different types). The implications of using this rating scale for different phenotypes need more elaboration.