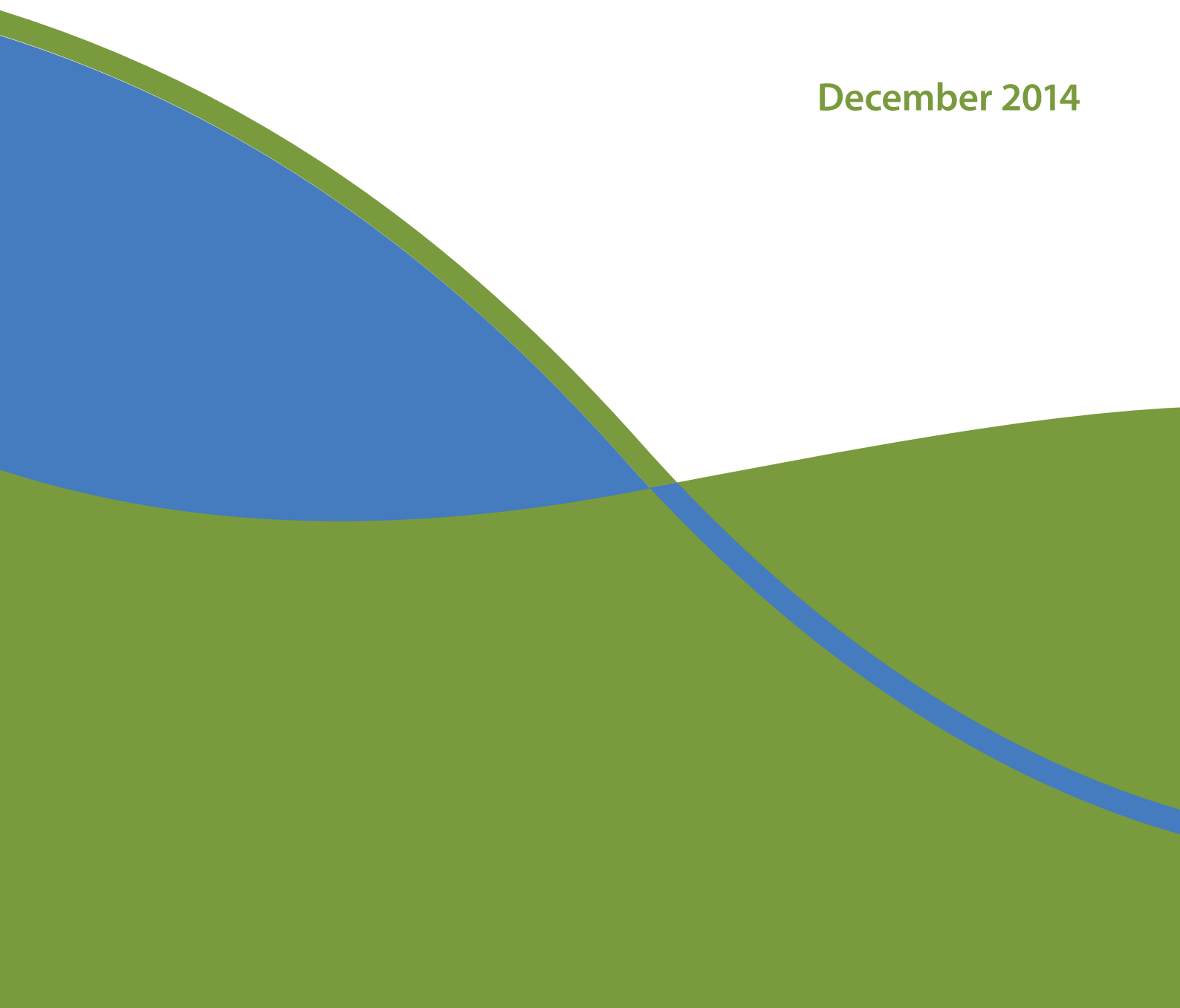


# Realising Genomics in Clinical Practice

December 2014



**Authors:** Alison Hall, Tom Finnegan, Corinna Alberg

## **PHG Foundation project team**

Corinna Alberg, Hilary Burton, Tom Finnegan, Alison Hall, Nina Hallowell,  
Mark Kroese, Jane Lane, Leila Luheshi, Sobia Raza

## **Acknowledgements**

The PHG Foundation is grateful for the expert guidance and advice provided by Dr Jo Whittaker and the internal and external steering groups (Appendix 6).

This paper can be downloaded from our website:  
[www.phgfoundation.org](http://www.phgfoundation.org)

### **Published by PHG Foundation**

2 Worts Causeway  
Cambridge  
CB1 8RN  
UK

Tel: +44 (0) 1223 761 900

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Correspondence to:  
[alison.hall@phgfoundation.org](mailto:alison.hall@phgfoundation.org)

How to reference this report:  
*Realising Genomics in Clinical Practice*  
PHG Foundation (2014)  
ISBN 978-1-907198-15-1

The PHG Foundation is an independent, not for profit think-tank (registered in England and Wales, charity No. 1118664, company No. 5823194), working to achieve better health through the responsible and evidence-based application of biomedical science.

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# Executive summary

Recent developments in genomic sequencing technologies have the potential to revolutionise the diagnosis and treatment of many diseases, particularly inherited diseases and cancers. Fast paced development and declining costs mean that the NHS is on the cusp of introducing new genomic sequencing diagnostic tests, including expanded next generation sequencing (NGS) gene panels, whole exome sequencing (WES) and ultimately, whole genome sequencing (WGS).

Together, these applications will form an important addition to existing genetic testing strategies: they promise faster diagnosis of inherited and *de novo* disease, particularly where simultaneous investigation of multiple genes replaces sequential investigation, resulting in lower sequencing costs per gene.

Improved knowledge will advance clinical care in due course, however the ability to investigate the whole exome or genome also brings significant challenges: sequencing generates huge amounts of data and understanding the health impact of the genomic variants that are identified is often complex and difficult.

*Genomic sequencing technologies have the potential to revolutionise the diagnosis and treatment of many diseases, particularly inherited diseases and cancers...The aim of the Realising Genomics project is to inform the optimal clinical implementation of these genomic technologies.*

The aim of the *Realising Genomics* project is to inform the optimal clinical implementation of these genomic technologies. This report identifies the broad range of ethical, legal, social and practical issues that will arise from using the technologies (*i.e.* expanded NGS gene panels using selected gene lists through to genome-wide sequencing technologies) within a clinical setting. It seeks to address these challenges by proposing a comprehensive set of recommendations for implementing these technologies in ways that improve healthcare while minimising potential harms.

## Background

The PHG Foundation's *Realising Genomics* project took place over two years from 2013 to 2014. It involved a wide range of stakeholders and international experts and was supported by an external steering group. Key ethical, legal and social issues (ELSI) raised by the introduction of these sequencing technologies were deliberated in five iterative workshops which informed the policy recommendations set out below. The first workshop identified the range of issues emerging from ELSI research on the use of these technologies, both in the UK and internationally. The second workshop considered the interface between clinical care and research which is becoming less distinct as a rapidly growing knowledge-base is populated by both activities and increasing numbers of patients cross the clinical / research boundary. The third workshop focused on likely changes to the patient pathway as these technologies

become entrenched in clinical care and explored how consent, disclosure of results and various technical aspects should be managed to optimise their effective implementation in the clinic. The fourth and fifth workshops focused on developing a framework for implementing these technologies using gene lists as a first-line approach. Working with key stakeholders, we formulated recommendations that help to minimise the ethical, legal and social challenges of translating these new NGS diagnostic applications into clinical care and ensure that they are implemented in a proportionate and responsible way.

## Summary of key findings

We have identified the recommendations that **need** to be addressed immediately in order for new diagnostic services using genomic sequencing to be implemented and delivered in an ethical and equitable manner. We have also identified a set of recommendations that **should** be implemented as a matter of urgency, in order to deliver these technologies in the most efficient manner.

One way of presenting our recommendations is in terms of the four ethical principles of beneficence, non-maleficence, autonomy and justice<sup>1</sup>. It is especially difficult to be certain that adopting a novel technology will do good (*i.e.* cause beneficence) rather than harm (*i.e.* cause maleficence) because of a lack of evidence about the scientific validity of the genetic variants that are detected, and the clinical utility associated with their detection. For this reason, one of our key recommendations is to restrict implementation of these novel NGS diagnostic technologies to deliberately target analysis and interpretation to disease associated genes consistent with the patient's presenting phenotype (R1). This can be done through developing gene lists based on phenotype (R3) through multidisciplinary expert groups (R4). Using this approach as a first-line test (R6), before undertaking analysis and interpretation of the whole exome or genome will help to avoid generating large volumes of data of uncertain benefit (R5). To support the interpretation of pathogenicity of genetic variants from NHS patients, an NHS Database needs to be set up (R12). Mandating deposition of variant, clinical and phenotypic data into this database whilst ensuring proportionate controls on access will help to create a robust and reliable database that serves the needs of NHS patients (R13).

The avoidance of harm (*i.e.* non-maleficence) was also addressed: a recurring theme concerned the volume of findings that might be generated, particularly uninterpretable findings (*i.e.* variants of unknown significance, VUS) and incidental findings (IFs) (potentially) associated with other diseases that are not relevant to the current diagnosis<sup>2</sup>. Disclosing findings without understanding their significance could cause anxiety and distress to patients and families, and delivering that information could strain limited clinical resources. Deciding whether and how to disclose information about IFs to patients may concern clinicians because patients may be wholly unprepared to receive this information if it has not been discussed during the consent process. Proposed solutions include developing consistent approaches to generating and interpreting these findings (R16) and disclosure to clinicians and patients (R17). Ensuring that new knowledge is available to inform interpretation (R16) and where appropriate, and if consent allows, shared beyond the NHS (R15) will help to make these systems more robust. The health benefits of actively searching for clinically actionable variants within selected genes (*i.e.* opportunistic screening) within clinical care are not currently proven and the harms are likely to outweigh the potential benefits (R5).

*We have identified the recommendations that **need** to be addressed immediately in order for new diagnostic services using genomic sequencing to be implemented and delivered in an ethical and equitable manner. We have also identified a set of recommendations that **should** be implemented as a matter of urgency, in order to deliver these technologies in the most efficient manner.*

One way to address these potential harms is to ensure that patients' autonomous choices are recognised through enhancing current processes for seeking consent: consent processes should include a thorough discussion of the impact, benefits, risks and uncertainties that may arise. The nature of the test; the generation, interpretation and disclosure of IFs and VUS (R7-9), the sharing of data (R11, 15) and the potential for reanalysis and recontact (R7, 10) are elements that should be explicitly addressed. Reanalysis of data and unsolicited recontact raise novel ELSI challenges, and engaging patients fully by offering an opt-out of recontact (R10) is a way of respecting patient autonomy.

As with any new technology, ensuring that access is fair and equitable is a key aspect of responsible implementation. Consistent approaches to patient referrals through gene lists (R1) and systematic approaches to reanalysis and recontact (R18) need to be developed. These must be supported by educational resources for healthcare professionals and patients (R22), and underpinned by robust mechanisms for evaluation (R24) and commissioning (R25). This package of measures needs to be put in place to ensure that these technologies are implemented in a responsible and ethical manner, and in ways that optimise their clinical utility for patients and families, minimise the potential harms associated with their use, and build public trust and confidence.

# Recommendations

## Recommendation 1

The NHS should adopt targeted analysis using gene lists following genome-based sequencing as an assay. This targeted approach will have greater clinical utility for the majority of clinical applications than approaches involving analysis and interpretation of the whole exome or genome.

## Recommendation 2

Use of genomic tests should be justified on a per-test basis, supported by clear, transparent and standardised referral criteria.

## Recommendation 3

Where clinically applicable, we recommend that NGS gene lists incorporating a core / standardised set of genes appropriate to the phenotype are routinely adopted.

## Recommendation 4

(A) Standardised evidence criteria should be developed for the selection and evaluation of genes in gene lists.

(B) Once these are agreed, mechanisms need to be developed for relevant experts in specified clinical areas 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 healthcare professionals and NHS scientists). These activities will need to be resourced.

## Recommendation 5

Bioinformatics search strategies should minimise the generation, interpretation and disclosure of IFs which are outside the scope of the clinical enquiry. This is on the basis that without sufficient evidence for the clinical utility of opportunistic screening, the potential harms are likely to outweigh the potential benefits.

## Recommendation 6

Clinical criteria should be developed for moving from targeted sequencing and analysis to using open sequencing and analysis as a second-line test. Clinical guidelines should also be developed for the use of open sequencing (exome- or genome-based) as a first-line test.

## Recommendation 7

It is the responsibility of the referring clinician to provide transparent information and to seek consent relating to targeted and open sequencing and analysis. This should include advising patients about the possible generation and significance of IFs and VUS, and establishing their views regarding recontact.

## Recommendation 8

The clinical consent process should include an explanation that IFs and VUS may be generated during genomic sequencing, that these may require further investigation, and that the test results may have implications for the patient's biological relatives.

## Recommendation 9

As part of the consent process, patients should be given the opportunity to express their views as to whether IFs generated from genomic sequencing should be disclosed to them. Where appropriate this might form part of a dialogue with clinicians. Disclosure decisions will be informed by clinical judgement.

## Recommendation 10

The possibility and nature of reanalysis necessitating future contact should be routinely covered in the initial consent process if this is part of the testing service (and if necessary supplemented by further discussions). Patients should be given the opportunity to opt-out of recontact. There should be transparency about what findings might be returned, how long after the initial episode of care contact might be made, who would contact the patient and likelihood of this arising, and how the patient may initiate contact.

## Recommendation 11

There must be transparency within the consent process regarding how sequence data are used. We recommend that the initial consenting process is clear that data will be routinely shared within the NHS.

## Recommendation 12

A secure, comprehensive, accessible NHS Database is urgently required that can underpin ongoing genomic sequence interpretation, improve clinical outcomes and support the needs of clinical services. This nationally accessible database should be considered an integral part of NHS genomic testing services and will need to be resourced. Any initiative should be long-term and sustainable.

## Recommendation 13

Deposition of data into the secure NHS Database **needs** to be (i) mandated through enhanced service specification, accreditation, and commissioning and (ii) supported by NHS England policies. Any compulsory data sharing must be consistent with existing regulatory frameworks, and address potential concerns about safeguarding privacy and identifiability.

## Recommendation 14

The most effective strategy to promoting data sharing will be to build on existing knowledge and systems (both nationally and internationally) and adapt this for the NHS.

## Recommendation 15

Systems and legal processes need to be put in place to allow the contents of the NHS Database to be shared more widely outside the NHS. In order to address proposed legislative changes, the optimal method of establishing a firm legal basis for sharing identifiable patient data beyond the clinical care of the patient would be to seek routine appropriate consent. This will contribute to building public trust.

## Recommendation 16

A NHS-wide data sharing mechanism should be established to help facilitate VUS interpretation.

## Recommendation 17

A national-level multidisciplinary committee should be established to develop standards for laboratories as to when to report VUS and IFs to referring clinicians. This body should also develop advice for clinicians as to whether and how to disclose IFs to patients.



## **Recommendation 18**

A systematic, evidenced-based approach should be taken to reanalysis and recontact. Standardised approaches should be developed through professional standards and guidelines.

## **Recommendation 19**

Ongoing ethical, legal and social science research and evaluation are needed to inform good practice, especially in areas where genomic sequencing technologies raise novel challenges: these include reanalysis, recontact, and the evaluation and reporting of findings.

## **Recommendation 20**

Urgent health economics analysis is required to demonstrate the circumstances in which genomic sequencing may be more cost-effective than competing technologies. This information may assist in prioritising how genomic sequencing is rolled out across clinical specialities.

## **Recommendation 21**

Systems and processes should be sufficiently dynamic and flexible to be able to respond to future developments, such as the need for increased IT infrastructure and storage as a result of a transition to routine WGS.

## **Recommendation 22**

Regardless of clinical specialty, all clinicians requesting diagnostic tests that utilise NGS sequencing will require support in order to deliver a safe and effective service for their patients. Developing core competences for ordering genomic testing should be explored: competences will need to encompass appropriate referral, consent processes and the interpretation of results.

## **Recommendation 23**

Public confidence is a vital element in securing the successful clinical implementation of novel technologies: it is therefore vital that claims made about their impact are realistic and that services are implemented in ways that are transparent and accountable.

## **Recommendation 24**

Systems for evaluating genetic and genome-based tests for use within the NHS need to be supported and developed further to enable timely and robust assessment. Standard operating procedures should be used to manage modest changes to sequencing and interpretation pipelines, and to the contents of gene lists.

## **Recommendation 25**

There needs to be an appropriate commissioning mechanism to consider the implementation and funding of genomic sequencing tests in a timely manner in response to evidence of their clinical utility. This will need to include arrangements for prioritising and managing access to testing, interpretation and follow-up.

# 1 Background

The use of genomic sequencing technologies in medical practice has the potential to revolutionise the diagnosis and treatment of many diseases, particularly inherited diseases and certain forms of cancer<sup>3,4,5</sup>. Although Sanger sequencing has been used for many decades with approximately 100,000 molecular diagnostic tests reported per year<sup>6</sup>, the use of next generation sequencing (NGS) technologies is more limited, with whole exome sequencing (WES) and whole genome sequencing (WGS) being largely confined to medical research in the UK. The focus of this report is the emerging use of an expanded range of NGS based tests for diagnostic purposes.

Whether these tests are for panels of genes (referred to as gene lists), WES or WGS they are collectively described as next generation sequencing (NGS) in this report. Historically, the limited implementation of genomic sequencing has been partly due to the clinical utility of WES / WGS being uncertain and costs unsustainable within publicly funded healthcare systems. However, over the last few years, this situation has undergone a rapid transformation<sup>7</sup>; plummeting sequencing costs mean that genomic sequencing is becoming economically viable and improved data quality and enhanced data analysis and interpretation has resulted in improved clinical utility. As a result, there is an urgent need to determine how NGS can be utilised most effectively to improve patient care within the UK NHS. In order to inform these developments, the PHG Foundation initiated a project in January 2013, *Realising Genomics in Clinical Practice* ('*Realising Genomics*'), to identify the broad range of ethical, legal and social issues (ELSI) likely to arise from the implementation of new genomic sequencing technologies in clinical practice and to generate recommendations for how these should be managed.

*...there is an urgent need to determine how NGS can be utilised most effectively to improve patient care within the UK NHS.*

This project built on the findings of the PHG Foundation's *Next steps in the sequence* report<sup>8</sup>, which provided a comprehensive overview of the potential clinical impact of WGS. A key component of that report was a review of the ethical, legal, and social implications of using these technologies in clinical settings. The authors were guided by four key questions:

- The extent to which new DNA sequencing technologies would *alter or augment* routine clinical practice in medicine and in population health in the short to medium term
- Novel ethical, legal, social and economic issues raised

- The implications of WGS for *diagnostic* services more generally
- The identification and mitigation of *operational barriers* preventing implementation.

*Realising Genomics focuses more explicitly on the ethical, legal and social issues highlighted by the Next steps in the sequence report...*

The principal conclusion of the *Next steps in the sequence* report was that NGS is likely to be used as a replacement for existing testing strategies in the short to medium term, and that sequencing and analysis will be used mainly for those applications where it offers clear clinical or cost benefits over existing tests. The report concluded that clinical bioinformatics expertise and infrastructure should be developed to ensure sufficient technical support for clinical interrogation of genomic sequence data and recommended that an evidence base of normal and disease associated variants be developed to allow clinical interpretation of genome-wide sequence data. It also identified a need for policy research on the changing roles and responsibilities of health services, healthcare professionals and patients, especially in relation to consent, disclosure and reanalysis of sequence data.

With *Realising Genomics* we focus more explicitly on the ethical, legal and social issues highlighted by the *Next steps in the sequence* report, and also address in more detail how the overarching recommendations to use targeted approaches supported by a robust evidence base and bioinformatics infrastructure might be developed with the aim of improving patient care. The scope, aims and objectives of the *Realising Genomics* project are set out in Chapter 2 and Appendix 3.

In inherited disease, the main purpose of using diagnostic technologies is to detect changes in germline DNA that cause disease, in order to make a diagnosis and to guide treatment and management. Traditionally clinical genetic scientists have used a combination of molecular genetic technologies, (targeting testing of specific regions of DNA for small variants consisting of one or more base changes), and cytogenetics (whole genome analysis to detect structural variation and copy number changes). A variety of technologies are used *e.g.* karyotype analysis, fluorescence *in situ* hybridisation (FISH) microarrays and many based on the polymerase chain reaction (PCR). Where a particular disease is suspected through a combination of clinical presentation and family history, it may be more effective to undertake a cheaper assay and targeted test, than to undertake genome sequencing. For less common conditions involving private mutations, Sanger sequencing has generally been used.

Development of new technologies has enabled the introduction of gene panel tests. These phenotypically driven panels allow testing of between two to around 1000 genes to assess multiple genes at one time for the diagnosis of one or more related disorders. They have the potential to offer a more cost-effective test with improved turnaround times and patient outcomes. More than 40 such tests have been recommended for NHS use across a range of specialties including cardiology, cancer, neurology, ophthalmology and renal medicine (UKGTN communication). WES and WGS are also being developed for clinical diagnostic use. They offer the ability to interrogate many more genes / DNA sequences in a single assay but the sensitivity and specificity of variant detection may not match that of more targeted methods. For more information about the scientific and technical basis of NGS technologies see Appendices 4 and 5. The choice of NGS diagnostic testing versus alternative testing strategies is addressed in Chapters 3 and 4.

## 1.1 Factors influencing wider clinical implementation and adoption

### 1.1.1 Ongoing technological advances

When *Realising Genomics* began in January 2013, NGS technologies were already an integral part of medical research in the UK with most major centres having access to genomic sequencing expertise. However a few UK centres have begun to incorporate WES into their clinical service, including Cambridge, Exeter, Leeds and Manchester [Dr Ruth Charlton (Appendix 7), personal communication].

In the Netherlands, the Department of Human Genetics at Radboud University Medical Centre, Nijmegen has developed the use of diagnostic testing using genomic sequencing by automating the pathway for handling samples for a range of applications (initially using targeted interpretation of exome sequences using NGS assays for lists of genes guided by the patient phenotype and subsequent interpretation of the whole exome sequence where appropriate). Increasing the numbers of genes that are sequenced and interpreted has resulted in improved diagnostic rates compared to Sanger sequencing undertaken in-house<sup>9</sup>. This model could inform how expanded genomic sequencing technologies might be organised within the UK.

### 1.1.2 Ethical issues arising from the use of NGS technologies: the role of autonomous choice

NGS has the potential to generate greater numbers of findings that are unconnected with the clinical enquiry, *i.e.* incidental findings (IFs), than previous techniques. The frequency of these findings will depend on how closely the clinical question is defined, and the strategies that are used to target the interpretation of the genome sequence. An associated question is whether patients should have a choice about whether these IFs should be reported back to them, a discussion that should take place as part of the informed consent process. There are concerns that the informed consent process, as it is currently conceptualised and undertaken, is inadequate for application to genomic medicine (Appendix 8)<sup>10</sup>. Advice from the American College of Medical Genetics and Genomics (ACMG)<sup>2</sup> initially mandated that patients offered clinical WGS have a set of 57 (later amended to 56) clinically actionable genes sequenced and interpreted, irrespective of patient age, including some adult-onset diseases. Recently this advice has been amended<sup>11</sup> to allow for patients to undergo WGS while opting-out of receiving IFs (disease associated or likely disease associated findings that are not apparently relevant to a diagnostic indication for which the sequencing test was ordered)<sup>2</sup>. In their recent policy statement the ACMG adopted the term 'secondary findings' to describe a subset of IFs that are serious and clinically actionable. We have chosen not to adopt that terminology in this report, as the term is not yet in extensive use in the UK. Despite this clarification from the ACMG, the question of how IFs should be handled in clinical settings remains a highly contentious and debated topic.

*There are concerns that the informed consent process, as it is currently conceptualised and undertaken, is inadequate for application to genomic medicine.*

### 1.1.3 The interface between research and the clinic

The rapid transition from research to clinical use has sometimes led to a lack of clarity amongst stakeholders about whether sequencing is being undertaken for clinical or research purposes. This is a key distinction, because it informs the ethical and legal principles that apply to the generation and governance of genomic data (as well as influencing the outputs of the sequencing process)<sup>12</sup>. In clinical genetics, there has been a close relationship between clinical and academic departments. There has also been a tradition of supplementing existing clinical diagnostic tests with as yet clinically unvalidated research-based tests, and then adopting these into clinical practice as their performance reaches the standards required for their validation as diagnostic tests. This also seems to be the pattern with applications using NGS technologies. The ambiguity of these practices is compounded by the high capital costs of acquiring sequencing machines and providing staff with sufficient expertise to run tests and interpret results, which has resulted in the occasional use of research equipment and staff for clinical purposes. During the *Realising Genomics* project, these interface issues increased in prominence, partly due to clinical sequencing being implemented in more research and clinical centres around the world, resulting in concerns about how this ambiguity might impact on patient care. As a result, an additional workshop exploring the impact of genomics on the boundary between research and clinical care was added (Chapter 2).

### 1.1.4 100,000 Genomes Project

In December 2012, the UK Government announced a major initiative to sequence 100,000 whole genomes from NHS patients over five years. This project is focused primarily on patients who might gain most from having their whole genomes sequenced, *i.e.* those with rare inherited diseases, where a cause for their condition has not been identified through existing diagnostic tests, and patients with certain types of cancers. It will include germline and somatic samples from cancer patients, and include samples from the patient and sometimes their close relatives, usually parents, for patients with rare inherited disease. A specially convened scientific committee has determined the types of patients who should be included, and the scope of recruitment remains under review in advance of the main wave of recruitment commencing in early 2015<sup>13</sup>. Primarily a research project, the key features of the 100,000 Genomes Project (100,000 GP) are that it aims to:

- Sequence the genomes of patients recruited from the NHS
- Promote genomics expertise
- Generate commercial investment in the UK and thus
- Provide a legacy for the NHS

As part of the 100,000 GP, processes and infrastructure will be put in place for obtaining consent from participants and for storing and handling samples and data. It is hoped that analysis and interpretation will take place through bespoke collaborations ('Clinical Interpretation Partnerships'). Safeguards to protect data and protect against privacy breaches include limitations on how users may access, process and extract patient data.

### 1.1.5 Public engagement and public trust

A general undercurrent of suspicion and mistrust about the extent of government surveillance of private individuals exists in UK society, as is exemplified by the press coverage of the Snowden affair<sup>14</sup>, the enactment of the DRIP regulations<sup>15</sup>, and publics' reactions to some government initiatives to collate and integrate individual health and social care data from multiple sources<sup>16,17</sup>. Given this context and the continuing need for ongoing data sharing, efforts to engage with patient groups and wider publics are vital to ensure public trust when implementing genomic sequencing technologies in clinical settings.

## 1.2 Summary scope and objectives of *Realising Genomics*

With these contextual issues in mind, *Realising Genomics* had a set of practical aims:

1. To identify the ways in which the adoption of diagnostic testing using WES and WGS in clinical settings within the NHS might change existing practice
2. To identify the ethical, legal, and social issues associated with these changes, whilst taking account of the ethical principles underpinning existing practice
3. To formulate practical recommendations that will support the implementation of NGS applications in clinical settings in the NHS

*Realising Genomics* has focused primarily on the ELSI issues arising from using genomic sequencing technologies in inherited diseases, rather than in cancers or infectious diseases. We recognise that using these technologies in the context of inherited diseases raises a distinctive set of issues that are not necessarily applicable to these other applications. The PHG Foundation is currently undertaking other work in these two areas.

## 1.3 Recommendation format

Each section of the report contains recommendations that have been developed through a combined process of research, analysis and stakeholder engagement. This process is described in greater detail in Chapter 2. Chapter 3 sets out the assumptions on which these recommendations were developed e.g. that for certain applications, using NGS technologies can be justified on the basis that they confer increased clinical utility. We have identified the recommendations that **need** to be implemented immediately in order for new diagnostic services using genomic sequencing to be implemented and delivered in an ethical and equitable manner. We have also identified a set of further recommendations that **should** be implemented as a matter of urgency, in order to be able to deliver these technologies in the most efficient manner. The process for developing the recommendations included explicit discussion during workshops, and endorsement of the principles by the *Realising Genomics* external steering group (Appendix 6) and the final wording by the PHG Foundation steering group.

## 1.4 Conclusion

Implementing an NGS genomic sequencing service involves attention to every aspect of the pathway from patient referral, to consent and sample acquisition, through sequencing, annotation, and interpretation to reporting. One major challenge to existing services and processes is the need to process, interpret and manage the unprecedented volume of genomic data that will be generated from the clinical implementation of diagnostic genome sequencing. *Realising Genomics* addresses these challenges by proposing specific recommendations that we believe should be adopted by policy makers in England and across the UK. It is premature to judge whether the infrastructure that will be put in place through the 100,000 Genomes Project could be repurposed to deliver some of the recommendations contained in this report, which is a matter for future policy development. The focus of this report is to establish a framework of recommendations that together will optimise NGS implementation and achieve better patient care and management in clinical practice.

*The focus of this report is to establish a framework of recommendations that together will optimise NGS implementation and achieve better patient care and management in clinical practice.*



## 2 Aim & method

The aim of *Realising Genomics* is to inform the effective clinical implementation of genomic technologies by identifying the broad range of ethical, legal, social and practical issues that will arise from using targeted and genome-wide sequencing technologies within a clinical setting.

### 2.1 Methodology

In order to achieve the project aim, key objectives were identified (Appendix 3). As part of the project we reviewed existing and emerging uses of NGS applications in clinical practice and other relevant projects within the UK (such as the 100,000 GP). In collaboration with stakeholders, we explored practical and conceptual issues linked to the introduction of an expanded range of tests using NGS technologies through reviewing patient pathways, information provision, consent, data sharing and return of results, to identify key ELSI issues and formulate recommendations for implementation.

The policy guidance and recommendations were developed through an analysis of the literature on the clinical implementation of NGS technologies and through a series of iterative stakeholder workshops that each had a specific focus.

An invited steering group, consisting of representatives from relevant stakeholder groups (Appendix 6) had the following terms of reference:

1. Finalising project objectives
2. Advising on the content of the project (including the workshops and the outputs from the workshops) and potential participants
3. Providing guidance on the policy outputs, including policy recommendations, as appropriate

This steering group met twice: at the initiation of the project in April 2013, to discuss the objectives of the project and programme of work and towards the conclusion of the project in October 2014, to consider draft recommendations. Members of the group also participated in some of the workshops.



## 2.2 The workshops

The aim of Workshop 1 (July 2013) was to identify the key ELSI emerging from research on the clinical implementation of NGS applications. Researchers from the UK, Europe and North America were invited to present their findings and discuss these with experts in the ELSI field. Given limited clinical implementation of NGS applications at that stage, a number of researchers presented their findings on the use of these technologies in a research setting as an indication of the types of issues that may arise when these technologies are implemented in the clinic (Appendix 8). The key challenges identified by the workshop were:

- The scale and complexity associated with large datasets, which might be addressed through developing appropriate bioinformatics pipelines to allow meaningful data feedback to clinicians and patients
- Developing consent processes that protect patient autonomy
- Providing education and training for health professionals and patients to support the introduction of these technologies into mainstream medicine
- Ensuring equity of access to these technologies and appropriate management of any ensuing healthcare needs
- The risks and benefits associated with using NGS technologies in the absence of clinical symptoms (*i.e.* using these technologies as opportunistic screening tools)
- The appropriateness of offering genomic testing (for late onset diseases) to asymptomatic children

*In Workshop 2 we examined the research-clinical interface and whether the boundary between these settings can or should be maintained as NGS technologies are applied in a clinical setting.*

In Workshop 2 (December 2013) we examined the research-clinical interface and whether the boundary between these settings can or should be maintained as NGS technologies are applied in a clinical setting. This distinction is significant from an ethical and legal perspective. Research and clinical care stem from different motivations. The primary objective of research is to test hypotheses and produce generalisable research findings, such as evidence of clinical utility, which may benefit society but which are of unproven individual benefit and may possibly even harm individual participants<sup>18</sup>. Thus researchers need to ensure that research participants have freely consented to taking part in research, and that they can withdraw at any time without compromising their clinical care. In contrast, the primary objective of clinical care is to treat the individual patient, requiring the physician to act in the patient's best interests. Technological developments in genomics are moving at such a rapid rate that this boundary is becoming blurred because novel technologies may be used in a research setting to supplement clinical care. It is often difficult for patients to distinguish these activities, particularly as they may receive diagnostic testing and treatment as part of a research initiative *e.g.* the Deciphering Developmental Disorders (DDD) project. While the rapid translation of research into clinical practice has contributed to blurring the boundary in recent years, the consensus of Workshop 2 was that the two activities should remain conceptually separate, and that extra efforts should be used to distinguish them in practice (Appendix 8).

*The key findings from Workshop 3 were that changes to the patient pathway are likely to be modest if NGS technologies are implemented in a targeted manner, thus simplifying the task of developing processes that are ethically acceptable and legally sound.*

In Workshop 3 (February 2014) we examined the patient pathway (*i.e.* the episode of care from initial referral to discharge from clinical services) and how this might change as a result of using an expanded range of NGS tests. The nature of the ELSI generated by the use of NGS (particularly WES / WGS) will depend on how broad the testing strategy is (*i.e.* both at the level of the individual, and also at a population level – the extent to which all those who might be ‘at-risk’ of disease can access the test). The ELSI generated will also depend upon what stage in the diagnostic process NGS is used and whether it is used exclusively by clinical genetics services or by a range of clinical specialties. Workshop participants also considered processes for: managing informed consent, deciding which results are sufficiently robust to be disclosed, and identifying the technical standards to optimise the effectiveness of these technologies in clinical practice.

The key findings from Workshop 3 were that changes to the patient pathway are likely to be modest if NGS technologies are implemented in a targeted manner, thus simplifying the task of developing processes that are ethically acceptable and legally sound. Evidence-based, harmonised clinical and laboratory standards need to be developed across the NHS to ensure equitable service provision and quality assurance. These should address consent processes, phenotypic characterisation and interpretation and reporting of variants, including VUS (*i.e.* genomic variants whose disease-causing potential is unknown) and serious IFs<sup>19,20</sup> (*i.e.* findings that are not related to the original clinical question, but which have clinical significance in that they are associated with a significant health problem which might be clinically actionable)<sup>21,22</sup> (Appendix 8). Appendix 9 describes a possible patient pathway that might be used for exome sequencing.

Workshops 4 and 5 (July 2014) focused on the main themes identified in the preceding workshops and the literature. The purpose of these workshops was to invite key stakeholders to consider these themes and develop a series of recommendations to optimise the clinical implementation of NGS technologies. Workshop 4 focused on an approach to sequencing using the iterative model developed in Nijmegen where, following sequencing, analysis and interpretation of the exome is initially limited to gene lists associated with the patient’s phenotype. If no diagnosis can be made after this targeted interpretation, the whole exome sequence is examined. The utility of this model for the UK was considered and recommendations made.

Workshop 5 developed recommendations on three topics: the use of expert committees to resolve issues around IFs and VUS; the development of a robust evidence base with which to interpret the clinical significance of variants sequenced; and the ongoing duty of care and whether patients should be recontacted in light of new medically relevant evidence.

The conclusions from all five workshops form the basis for the recommendations presented in this report.

## 2.3 Workshop delegates

Workshop attendees were invited on the basis of their expertise in the topics explored at each workshop and their interest in ELSI. As a result, some individuals were invited to more than one workshop (Appendix 7). Since the purpose of the workshops was to develop a comprehensive overview of a topic and develop recommendations, it was important to ensure that the delegates were representative of the major stakeholder groups, including: clinical geneticists, genetic counsellors, non-genetics clinicians with an interest in NGS technologies, molecular laboratory scientists, patient organisation representatives, researchers, bioethicists, lawyers with a particular interest in genomics related to ELSI and policy makers.

In addition to these key stakeholders, for the final two workshops we specifically invited chairs or chair-elects from the UK's main key professional bodies (BSGM, ACGS, JCGM and the Medical Genetics Clinical Reference Group) and delegates from the major stakeholder organisations (including Genomics England) so that these delegates could provide a view from the organisation they represented on the recommendations being developed. These delegates were also asked to suggest how their organisation might take forward recommendations identified at the workshops.

### 2.3.1 Method for developing recommendations

In the final two workshops we focused on developing a series of recommendations on areas where practice could be optimised. The method for developing recommendations was as follows: the first part of each workshop comprised a number of presentations. Following small group discussions on designated topics, each group developed a prioritised list of recommendations. These were presented back to the entire group for further discussion and a consensus reached about the topics that needed to be developed into final recommendations. The principles underpinning these recommendations have been endorsed by the external steering group, and wording ratified by the PHG Foundation steering group.

# 3 Underlying assumptions

Our recommendations are based on several underlying assumptions, which we set out below.

- A. Within publicly funded healthcare systems resources are restricted. Increasing demand for NGS diagnostic services and healthcare seems likely<sup>23</sup> as new interventions and technological developments become available. The context of an ageing population<sup>23</sup> and rising expectations about the contribution of healthcare systems to maintaining a healthy population will also generate additional demands<sup>24,25</sup>. These new technologies and services need to be cost-effective and efficient in order to secure funding. In the context of providing a clinical service within a publicly funded healthcare system, these objectives may be most likely to be met through targeting treatments to those who are likely to benefit the most, thus maximising cost-effectiveness and improving health outcomes and patient experience.
- B. In the short-term, for some patients, where phenotype and family history suggest that the condition is genetic, single-gene tests will continue to be the most appropriate testing strategy. The remainder of this report addresses how NGS technologies, including NGS assays of gene lists and WES / WGS, may be implemented once a decision has been made that single-gene testing is not appropriate.
- C. In any individual case, the sampling strategy will have an impact on the clinical utility of the findings that are generated using NGS technologies. For example, where the purpose of testing is to diagnose a condition in an affected child, comparing both parental genomes with those of the child through trio testing can be very effective in identifying novel putative pathological variants<sup>26</sup>. The extent to which trio sampling is a useful strategy to identify disease associated variants depends on the inheritance pattern of the condition being investigated. In the case of *de novo* conditions, it markedly reduces the number of variants that require further investigation as only variants occurring in the child and not the unaffected parents require further examination to determine whether they are causal<sup>27</sup>. However, as trio sampling involves analysis of parts of the parental genome, this may generate pertinent findings and IFs for the parent. Although, in many cases, trio sampling may be the most effective sampling strategy on the basis that it may increase the clinical utility of the test and improve test performance, there are ethical concerns about restricting access solely to trios of parents and children. In some cases this could result in inequitable access to testing as samples will not be available from both parents for a significant proportion of children<sup>28</sup>. Thus in deciding a sampling strategy within a clinical service, the expected clinical utility of the test needs to be balanced against the ethical requirement for distributive justice.

- D. Selecting genes for analysis and interpretation that are associated with disease development and specified phenotype will generate fewer VUS and IFs.
- E. The choice of using WES over WGS will change as sequencing costs decrease<sup>29</sup> and bioinformatics approaches become more automated, meaning that less time is required to filter and interpret large amounts of data.
- F. This report addresses clinical genomic sequencing services in England. In some cases it is generalisable to Wales, Scotland and Northern Ireland, although different regulations may apply.
- G. Equitable patient access to the appropriate range of sequencing technologies and high quality interpretation of sequencing should be an aspiration for the development of NGS-based services in the NHS. Family members who live in different areas should receive consistent results, based on a uniform, high quality evidence base.
- H. Well-curated, shared databases underpinned by mandatory deposition of data will support this service, and later in this report we discuss how these objectives might be achieved.

These assumptions have been developed through multidisciplinary discussion within the PHG Foundation and although informed by workshop participants, may not represent the views of all workshop participants.

### 3.1 Impact of WES / WGS on the patient pathway

Other pre-requisites for a consistent, harmonised and equitable service include ensuring that there is transparency about how patients might access these technologies, and some degree of standardisation of how WES / WGS are used. This involves charting existing patient pathways, and understanding how incorporating WES / WGS into these pathways might change practice or raise novel ethical issues. In Workshop 3 on patient pathways we explored the consequences of changes for: the consent process, arbitrating on whether variants are disease associated and the disclosure of variants including IFs. A figure setting out the patient pathway incorporating NGS gene panels / WES / WGS is set out in Appendix 9. Each of these aspects is explored in greater detail in subsequent chapters.

*Equitable patient access to the appropriate range of sequencing technologies and high quality interpretation of sequencing should be an aspiration for the development of NGS-based services in the NHS. Family members who live in different areas should receive consistent results, based on a uniform, high quality evidence base.*

## 4 Responsible implementation

In the remaining chapters we propose a framework for implementing expanded genomic sequencing in the NHS. The key objective of this framework is to achieve the potential benefits from these technologies whilst fully upholding important ELSI principles which underpin professional healthcare practice. We describe this as ‘responsible implementation’.

Increased use of genomic and other ‘omic’ technologies may help increase the numbers of patients who receive a diagnosis (‘the diagnostic yield’)<sup>9</sup> and provide earlier or more accurate diagnoses. At present, there is limited evidence about the cost-effectiveness of WGS / WES-based diagnostic services and whether these will result in improved health outcomes or increased demand for care and treatment, including access to reproductive technologies (such as pre-implantation genetic diagnosis).

There are disadvantages in generating high volumes of genomic information through genome-wide testing approaches. In particular, as the proportion of the genome analysed increases, the likelihood of identifying genomic variants that are difficult to interpret increases proportionately. In most cases, the optimal testing strategy should balance the likelihood of isolating the pertinent variant(s) with the risk of identifying a number of plausible candidate causal variants that cannot be distinguished from one another, leaving a patient without a diagnosis. Typically, the solution is to use a targeted genetic test, which analyses only a single candidate gene (Chapter 3, Assumption B), or where there is phenotypic or genotypic heterogeneity, a gene list, in which a number of genes are investigated in order to identify the causal variant. These ‘targeted’ approaches strike a pragmatic balance between maximising clinical utility and minimising the harms associated with a less focused approach. Occasionally, a broader testing strategy might be selected if it is warranted by the phenotype and the patient’s clinical needs e.g. for multi-system disorders (Chapter 5).

*These ‘targeted’ approaches strike a pragmatic balance between maximising clinical utility and minimising the harms associated with a less focused approach. Occasionally, a broader testing strategy might be selected if it is warranted by the phenotype and the patient’s clinical needs e.g. for multi-system disorders.*

The patient’s disease characteristics and symptoms (the phenotype) should guide the application of these technologies in an efficient and effective manner. Consistency is required in the way clinical phenotypes are described and recorded - healthcare professionals will need training and support to undertake this task. Additional data from other sources including histology or other types of patient record may also be required to undertake effective genomic analysis.

Given the assumptions outlined in Chapter 3, we believe that the use of targeted NGS approaches has the potential to deliver cost-effective and improved patient care while minimising the burdens associated with less targeted approaches (e.g. WES / WGS) which may result in overdiagnosis and the generation of VUS and IFs.

## Recommendation 1

**The NHS should adopt targeted analysis using gene lists following genome-based sequencing as an assay. This targeted approach will have greater clinical utility for the majority of clinical applications than approaches involving analysis and interpretation of the whole exome or genome.**

At an individual patient level, the choice to order a genomic test must be in the best interests of the patient. In order to avoid variability in sequencing provision across England and Wales, transparent criteria are needed to support the referral process and guide clinicians in understanding outcomes and interventions during sequencing. The clinical question and agreed referral criteria should guide the application of targeted exome sequencing / WES / WGS in every case.

## Recommendation 2

**Use of genomic tests should be justified on a per-test basis, supported by clear, transparent and standardised referral criteria.**

Targeted interpretation of the genome minimises the potential for generation of VUS and IFs, facilitates a consistent and harmonised approach between service providers, and has the greatest potential to deliver relevant clinical information at reasonable cost. In the short term, sequencing the whole exome and then using filters for interpretation guided by phenotype (i.e. a 'gene list' approach) has been assessed as being ethical, proportional and feasible. It is the optimal way of providing a standardised service that is of a consistent quality.

## Recommendation 3

**Where clinically applicable, we recommend that NGS gene lists incorporating a core / standardised set of genes appropriate to the phenotype are routinely adopted.**

In many cases there will be a trade-off between generating the maximum amount of potentially useful information and the feasibility of sequencing (in terms of sequencing costs and other bioinformatics resources) and interpreting the entire genome. Curtailing the scope of sequencing and interpretation to a narrow set of known disease-related genes could result in a system which allows for little flexibility (as new gene / disease associations are discovered and confirmed), and also might limit how local expertise in particular disease areas or local populations might improve diagnosis and treatment.



*A national expert committee should be appointed to develop standardised criteria for inclusion of genes into gene lists. Following this process, mechanisms should be put in place for each clinical area to identify a set of 'consensus genes' on the basis of these nationally agreed set of criteria.*

Processes for constructing, curating and implementing gene lists were debated in Workshop 4, and there was strong support for using a standardised process for developing gene lists for different clinical areas driven by patient phenotype. Using a standardised approach has the advantage of transparency, accountability and ultimately will lead to a consistent service being offered within disease areas and across the NHS.

A national expert committee should be appointed to develop standardised criteria for inclusion of genes into gene lists. Following this process, mechanisms should be put in place for each clinical area to identify a set of 'consensus genes' on the basis of this nationally agreed set of criteria. Groups of experts within each clinical area, should have responsibility for all gene lists within its remit. These gene lists constitute the national standard tests that should be provided across the NHS: the UK Genetic Testing Network (UKGTN) could be involved in this process. The gene lists for each clinical area should be regularly curated and updated, so that the genes within the list are clinically relevant. Using core gene lists would indicate which genes are disease-causing and variants within them would be evaluated for their likely pathogenicity in the context of the patient's phenotype.

These expert committees should operate in a dynamic and flexible fashion and not be unnecessarily bureaucratic. They should include representation from all relevant stakeholder groups including: healthcare professionals, researchers, and NHS scientists. The criteria for gene selection should be transparent and the members of these committees should be accountable to wider stakeholder groups; this is necessary to ensure that all stakeholders invest and trust in the process by which gene lists are developed. Since development of the gene lists and subsequent curation is likely to be laborious and time consuming, sufficient resources will be needed to support this process.

Notwithstanding this standardisation, mechanisms need to be developed for those patients falling outside existing phenotypic classifications to access multiple gene lists, bespoke focused analysis relevant to their phenotype or to proceed immediately to whole genome analysis, if clinically appropriate. This is necessary to ensure equitable access to NGS based tests. There should also be some flexibility for a referring clinician to order tests that deviate from standard practice on the basis of the individual patient's clinical need and best interests. If this approach is adopted, the clinician will be responsible for reporting results and IFs relating to these genes to the patient.

## **Recommendation 4**

**(A) Standardised evidence criteria should be developed for the selection and evaluation of genes in gene lists.**

**(B) Once these are agreed, mechanisms need to be developed for relevant experts in specified clinical areas 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 healthcare professionals and NHS scientists). These activities will need to be resourced.**



# 5 Choosing a sequencing and interpretation strategy

This chapter explores the circumstances in which it may be appropriate to widen the scope of genomic analysis and interpretation beyond the targeted core / minimum set of genes to the entire exome or genome. It makes recommendations for how this 'open sequencing' approach should be implemented in practice.

## 5.1 Opening the exome or genome

'Open sequencing' describes the process where a whole exome or whole genome is interrogated for sequence changes. This results in many more variants being detected than in a targeted approach. When large numbers of variants are identified, a bioinformatics prioritisation process is required to identify variants of interest. The prioritisation process will vary according to clinical application and the variability of the population presenting with a certain phenotype. This process may also involve the deliberate exclusion of known clinically actionable genes on the basis that they are not relevant to the clinical question.

## 5.2 Rationale for open analysis

An increasing number of UK centres are adopting WES and interpretation for both research and clinical use [Dr Ruth Charlton (Appendix 7), personal communication] but WGS is largely confined to research settings, where identifying novel, potentially disease associated variants is a primary objective. However in clinical settings within mainland Europe, some centres are offering WGS and interpretation as a first-line test on the basis that the more comprehensive sequencing coverage ultimately results in improved diagnostic yield<sup>30</sup>. In Workshops 3, 4 and 5 we specifically asked delegates to consider how patient pathways and management would need to change if WES or WGS were to be adopted as a routine first-line diagnostic test.

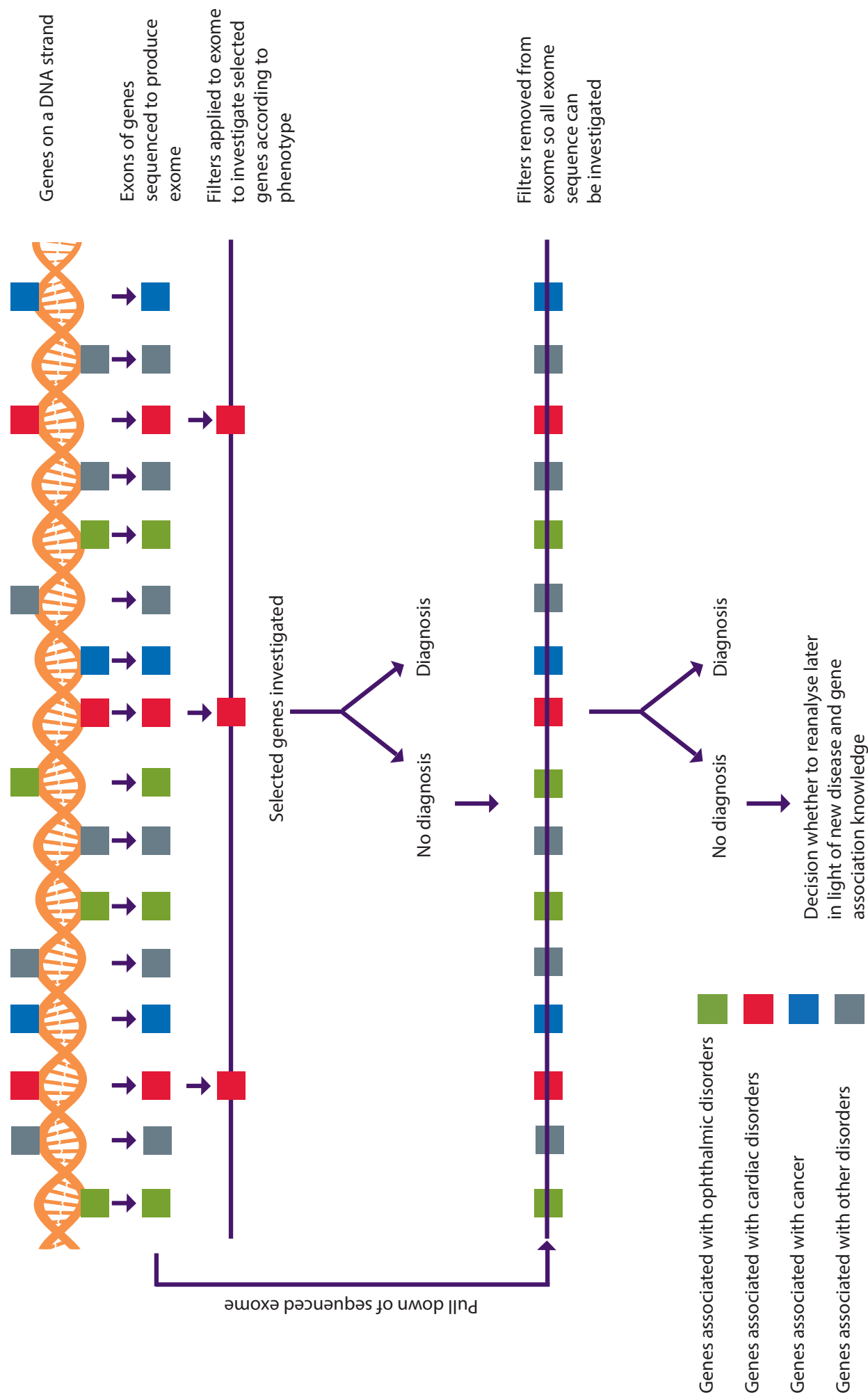
The overwhelming consensus in the workshops was that within publicly funded healthcare systems such as the NHS, it is not economically feasible to implement routine diagnostic WES and WGS for all patients with rare diseases in the short to medium term. However, a number of centres are developing strategies involving WES and WGS as a first-line approach for some patient groups in order to preferentially identify those variants which are most likely to be associated with disease<sup>26</sup>. If used as a routine first-line diagnostic test (particularly outside clinical genetics practice), changes to patient pathways and management would be required together with access to specialist clinical genetics expertise, laboratory scientists, bioinformaticians and genetic

counsellors to assist with interpretation and disclosure. In the short-term, open analysis approaches seem likely to be offered as a second-line test where there is potential for increased clinical utility. This might be where the patient's phenotype does not suggest appropriate gene lists, or there is extensive genetic heterogeneity or where the relevant gene lists have been used or exhausted such that the use of a whole exome or genome approach satisfies an unmet diagnostic need.

### **5.3 Rationale for open sequencing and interpretation as a first-line test**

Interpreting the entire exome or genome could be considered as a first-line test where there is not a suitable single-gene test or gene list available. This is likely to be the case when the range of potential phenotypes and associated genotypes is highly heterogeneous and underdetermined (such as for intellectual disability). For some genetically heterogeneous conditions the diagnostic yield from gene lists is low<sup>9,30</sup>. In such cases an examination of the whole exome or genome may increase the diagnostic yield. Using an open approach may also be justified in infants or young children where there is need to confirm a tentative diagnosis based on an incomplete phenotype (through age and immaturity)<sup>31</sup>. Figure 1 represents a targeted sequencing approach followed by open sequencing.

Figure 1: Targeted sequencing followed by open sequencing



*Since reporting VUS to patients has little potential to benefit and may cause anxiety, they should not be reported. As IFs are by definition unrelated to the clinical presentation, testing for and disclosing these findings is ethically problematic...*

## 5.4 Harms associated with an open analysis approach

The main harms arising from an open approach (an exome or genome wide approach) are that sequencing and interpreting the entire exome or genome is likely to generate larger numbers of VUS<sup>7,32,33</sup> and also increased numbers of IFs compared to more targeted sequencing<sup>34</sup>.

Resolving whether VUS are pertinent to the patient's condition is challenging and time-consuming<sup>35,36</sup> and currently the NHS lacks the resources to be able to do this on the increased scale that might be required once these technologies are introduced more routinely. The research literature estimates that exome sequencing results in the identification of a large number of variants that could require analysis and interpretation<sup>37</sup>, but in practice these are managed through bioinformatics algorithms resulting in a limited number of variants. Each variant requires laboratory and clinical time for consideration as well as time to identify whether it should be fed back to the patient. Since reporting VUS to patients has little potential to benefit and may cause anxiety, they should not be reported. As IFs are by definition unrelated to the clinical presentation, testing for and disclosing these findings is ethically problematic, and there has been extensive debate in the clinical and academic literature about how best to respond<sup>38,39</sup>. An IF in a child may indicate unanticipated disease in a parent since genomic sequencing strategies typically involve comparison between genomic sequences from an affected child and their parents. Finding unanticipated disease has potential to cause anxiety and reproductive dilemmas.

Most knowledge about the risks attributed to disease associated mutations is the result of experience with symptomatic individuals or research on small numbers of families. The level of risk in an asymptomatic individual who has no family history of disease which might be caused by the potentially disease associated variant is less clear than where there is a strong family history of disease (where the risks of disease emerging might be greater)<sup>40</sup>. In the former case, the advice given to the asymptomatic bearer of an IF is likely to be less accurate. For some diseases there may be a different prevalence rate in symptomatic individuals with a disease associated variant compared to asymptomatic individuals with the same variant.

Proactively searching for known clinically actionable genes in patients who have undergone clinical WES or WGS constitutes opportunistic screening. As described above, the benefits and harms associated with pathological variants in asymptomatic individuals who have no family history may be more difficult to determine. The likelihood of benefit or harm arising from opportunistic screening of this type is highly dependent on context and more empirical evidence is needed. From an ethical perspective, various commentators have justified opportunistic genomic screening on the basis of developing an ancillary care environment<sup>41</sup> or duty to rescue<sup>42</sup>, but in the context of a resource constrained publicly funded health service, such as the NHS, there are opportunity costs in actively searching for clinically actionable variants which are outside the scope of the clinical enquiry. Furthermore, providing access to opportunistic screening for clinically actionable variants could be regarded as inequitable, because only those with a pre-existing but unrelated clinical problem would access screening.

For these reasons, contrary to the ACMG recommendations that a minimal list of known clinically actionable genes should be actively generated in all patients undergoing clinical genomic sequencing<sup>2,11</sup>, we strongly recommend that bioinformatics search strategies (annotation and variant calling) should minimise the generation of these findings through the purposive exclusion of known clinically actionable genes that lie outside the scope of the clinical enquiry. At this time the potential harms associated with active searching for these variants are likely to outweigh the potential benefits.

## Recommendation 5

**Bioinformatics search strategies should minimise the generation, interpretation and disclosure of IFs which are outside the scope of the clinical enquiry. This is on the basis that without sufficient evidence for the clinical utility of opportunistic screening, the potential harms are likely to outweigh the potential benefits.**

Interpreting exomes and genomes to decide which IFs and VUS should be reported to patients is challenging and can be time consuming. This approach necessitates a consent process which enables patients to make an informed decision about whether to undergo such testing and to understand the potential benefits and risks involved, including disclosure of results. These issues will be addressed in Chapter 6.

## 5.5 Conclusion

For the majority of applications, a targeted approach using gene lists will offer optimal clinical utility. However, for some clinical applications, an open analysis approach may offer greater clinical utility than a targeted approach using gene lists. Therefore, it may sometimes be appropriate to utilise open sequencing and analysis as a first-line test. This approach will inevitably generate more potentially pertinent findings that are difficult to interpret (*i.e.* VUS), as well as more IFs. Bioinformatic strategies should minimise the generation of known clinically actionable IFs and VUS. The potential benefits and risks of using an open approach to sequencing and analysis need to be appraised for each potential application.

## Recommendation 6

**Clinical criteria should be developed for moving from targeted sequencing and analysis to using open sequencing and analysis as a second-line test. Clinical guidelines should also be developed for the use of open sequencing (exome- or genome-based) as a first-line test.**

## 6 What needs to be done?

A number of prerequisites need to be in place in order to create a robust, effective service, which realises genomic sequencing in an ethically responsible manner within the NHS. Prerequisites include the need for transparency, the development of a meaningful consent process and the establishment of data-sharing systems and practices to enable proper core gene list development and use.

### 6.1 Consent

The role of consent and the adequacy of existing processes were extensively debated throughout the *Realising Genomics* project. In the following sections we make general recommendations concerning consent in the context of clinical genomic sequencing. In this report we are not concerned with the theoretical underpinnings of consent in a medical context, including the protection of bodily integrity, but with the practical aspects of how clinical sequencing might affect existing consent processes in clinical practice.

In common law jurisdictions the procedural importance of consent is derived from its ability to act as a defence against unlawful touching<sup>43</sup>, although other legal mechanisms exist to permit medical treatment, such as the common law principles of necessity or best interests in England, or through primary legislation. (There is a wider philosophical point regarding the relationship between consent and the nature of autonomy that is too detailed to consider here.) Consent is regarded as valid where the patient is competent, informed and when it is voluntarily given<sup>44</sup>. Patient consent to treatment is one of the key elements of clinical practice. The welfare and the best interests of the patient are at the heart of a clinical encounter.

In the UK, within a clinical genetics setting, the nature of the consent process varies from patient to patient, and is based on the judgement of the clinical geneticist or genetic counsellor.

The implementation of NGS test services in clinical practice raises well documented challenges to the consent process<sup>45</sup>. As a clinical intervention, sequencing is governed by the common law and therefore requires that the patient is informed in general terms about the nature and purpose of the intervention, the consequences of not proceeding, and the risks and benefits of going ahead. These are relatively uncontroversial requirements.

Aside from consenting to the acquisition of the initial tissue sample, the consent-relevant elements of the sequencing process concern the data generated from that tissue and the uses to which those data will be put<sup>46</sup>. This includes issues relating to:

- Potential generation of IFs and VUS
- Reanalysis of data and recontact of the patient following reanalysis
- Further use of the data derived from the assay and the test (e.g. for research, audit, service improvement and commercial uses)
- The possibility that the results of the test might be inconclusive

These elements are not unique to clinical sequencing. IFs are a common feature of medical imaging and data relating to interventions and tests have long been used for the purposes of audit and commissioning. Nevertheless they are important, given the potential volume of findings, the probabilistic nature of the results, and the potential for indefinite storage and fresh interpretation over time.

## Recommendation 7

**It is the responsibility of the referring clinician to provide transparent information and to seek consent relating to targeted and open sequencing and analysis. This should include advising patients about the possible generation and significance of IFs and VUS, and establishing their views regarding recontact.**

The volume of findings likely to be generated from sequencing, the potential diversity of findings, and the potential for successive reanalysis of sequence data through bioinformatics methods rather than re-sequencing, has prompted concerns about the challenges to the consent process raised by WES and WGS<sup>10,47</sup>. Moving from targeted to open analysis increases the likelihood of generating more VUS and IFs which may also be of relevance to family members of the presenting patient. Adopting a step-wise approach to genomic sequencing and analysis, consisting of targeted analysis of gene lists, followed, only if necessary, by open analysis as a second-line test, therefore has the potential to simplify the consent process. Reserving open analysis for situations where targeted analysis has been inconclusive will potentially reduce the numbers of VUS and IFs generated and interpreted.

In Workshops 4 and 5 there was disagreement as to whether the clinical consent process for this approach should be single- or multi-stage. The potential benefits and drawbacks of both were discussed. A single stage process could cover in one consultation patient consent for both the targeted and open analysis, and also discuss the possibility and implications of IFs, VUS, and recontact. A single-stage consent process might, for example, help limit the expenditure of time and resources, and minimise disruption to patients, but also might have the disadvantage of being difficult to understand if too long or fail to provide sufficient detail and explanation if too brief.

A multi-stage approach could be structured so as to seek outline consent for both interventions during the initial session (and offer an opportunity for the patient to opt-out of open analysis) and subsequently following targeted analysis, explain the outcome of the targeted sequencing and seek explicit consent for open analysis if the targeted analysis did not provide a diagnosis. Multiple stages could help avoid the possibility of a single but extremely long and complex initial consultation, and could ensure that detailed information is only provided to the patient if the need arises (*i.e.* if the analysis and interpretation moves beyond targeted analysis). The use of more than one session could allow additional information to be provided in greater detail in an easier to understand format. However mandating more than one 'formal' consent session does not reflect the clinical realities of limited time and resources.

We concluded that a flexible approach which takes account of the context is preferable, wherein only one 'formal' consent session takes place, but patients are offered the opportunity to have a dialogue (*e.g.* letters, phone calls) with the clinical team following the first-line test, especially if they do not wish to learn about specific IFs. An additional consultation might take place if the decision is made to progress to open sequencing and analysis and the patient has specific concerns. Any such additional consultations should not be mandated, but left to local services and relevant clinicians to develop.

### 6.1.1 IFs and VUS

Part of the professional responsibilities of a physician is to inform their patient of risks arising from an intervention<sup>48</sup>. In the case of clinical sequencing, two of the most important elements requiring explanation are that the test might 1) generate IFs that are relevant to future health but which are not part of the clinical purpose of the test; and 2) identify VUS – sequence variants for which disease risk associations are not known. Open sequencing and analysis has the potential to generate more IFs and VUS than targeted approaches<sup>7,19</sup>.

In the case of NGS particularly WES / WGS, decisions about whether to inform the patient of IFs indicating risk of disease can be difficult if the risks associated with a disease-causing gene are unclear<sup>12</sup>. IFs identified through genomic sequencing, like other testing technologies that detect conditions with strong heritability, may have implications for other family members<sup>12</sup>.

Given their uncertain nature, VUS should not be routinely disclosed by doctors to their patients. However, disclosure may be necessary where more information (*e.g.* family history information) is required from the patient in order to help interpret VUS. It is for this reason that the consent process should cover both the possibility of the generation of VUS and the potential that disclosure will be necessary in some circumstances.

## Recommendation 8

**The clinical consent process should include an explanation that IFs and VUS may be generated during genomic sequencing, that these may require further investigation, and that the test results may have implications for the patient's biological relatives.**

*We concluded that a flexible approach which takes account of the context is preferable, wherein only one 'formal' consent session takes place, but patients are offered the opportunity to have a dialogue with the clinical team following the first-line test.*



Even if bioinformatics search strategies, such as the use of targeted analysis, minimise the generation of IFs and VUS, they may still arise (Recommendation 5). Professional guidance is needed to guide laboratories regarding the types of IFs and VUS that should be routinely disclosed to the referring clinician. Existing professional guidance and legal precedent suggests that the ultimate decision about disclosure of IFs should rest with the referring clinician on the grounds that clinical judgement may guide whether disclosure is in the patient's best interests. This should be supplemented by new national recommendations and guidance referred to in Recommendation 17. If VUS and IFs fail to meet minimum thresholds it is ethically justifiable for laboratories to choose not to report them on the basis that their likely impact is uncertain.

## Recommendation 9

**As part of the consent process, patients should be given the opportunity to express their views as to whether IFs generated from genomic sequencing should be disclosed to them. Where appropriate this might form part of a dialogue with clinicians. Disclosure decisions will be informed by clinical judgement.**

### 6.1.2 Recontact

As knowledge is developed to facilitate better interpretation of sequencing data, there is the possibility (and potential utility) of contacting patients with reanalyses of their assay data. This could occur some years after the initial consultation, and could generate anxiety if patients are recontacted without prior warning. There is little consensus regarding how, and under what circumstances, recontact should take place. The key problem is one of thresholds: what type of results should be returned? What should trigger fresh analysis? How often should analyses be done? What time limits should be applied? These questions are considered in more detail in Chapter 7.

## Recommendation 10

**The possibility and nature of reanalysis necessitating future contact should be routinely covered in the initial consent process if this is part of the testing service (and if necessary supplemented by further discussions). Patients should be given the opportunity to opt-out of recontact. There should be transparency about what findings might be returned, how long after the initial episode of care contact might be made, who would contact the patient and likelihood of this arising, and how the patient may initiate contact.**

### 6.1.3 Access to data

There is considerable debate about how data generated by clinical sequencing should be used. Should it be available for research, audit and commissioning purposes?

NHS patients have a right to be informed about how their personal information is used and can object to the use of their identifiable confidential information beyond their own care. These objections must at least be considered by the NHS and, if they are not honoured, patients have the right to be told why, including the legal basis for the decision<sup>49</sup>.

*Improved data sharing through a managed access NHS data resource is a prerequisite for providing a safe, effective WGS service.*

Downstream use of data should be consistent and compliant with the consent taken at time of testing. Seeking patients' views on the further use of data derived from tests is one way of respecting patient autonomy, but autonomy should not be treated as absolute. There are other very important interests at stake: primarily, the public interest in using patient data to build an evidence-base to facilitate the delivery of better and more consistent care across the NHS. For this reason our view is that no right of opt-out should be offered to patients for the use of their data within the NHS. Chapters 7-9 address the construction of an evidence base, data deposition and data sharing in more detail.

## Recommendation 11

**There must be transparency within the consent process regarding how sequence data are used. We recommend that the initial consenting process is clear that data will be routinely shared within the NHS.**

## 6.2 Developing a database for genomic interpretation

Chapters 4 and 5 outlined the rationale for adopting a systematic targeted approach to genomic sequencing. Improved data sharing through a managed access NHS data resource is a prerequisite for providing a safe, effective WGS service for a number of reasons:

1. **Interpretation:** Once WES / WGS sequencing is introduced into the NHS as part of routine clinical care for some applications, there is likely to be an initial increase in the number of potentially disease associated variants that are identified and in the numbers of VUS that require further interpretation and assessment using functional and other tests. Interpretation may also require accessing contextual data from family members, inheritance patterns, or other information. Sharing this data will be necessary to allow clarification of the status of VUS and improved test development. It will facilitate the construction and evaluation of bioinformatics pipelines, ensure that patients access standardised tests and achieve maximum clinical utility from limited sequence data.
2. **Develop gene lists:** It will be necessary to share variant data, pathogenicity and some additional information (including relevant phenotypic information) in order to generate evidence about the impact of individual genes and to construct the gene lists used for targeted approaches. The criteria for including a particular gene or variant within a gene list are likely to include multiple, independent citations within peer reviewed publications and existing databases: evaluating and interpreting those multiple citations will inevitably require data sharing between collaborators and participating centres in order to classify the extent of disease associated with individual genes and variants<sup>32</sup>.
3. **Quality assurance:** As expanded clinical NGS applications are adopted, there will be an increasing need to share data about the sequencing, annotation and interpretation processes including sequencing platform, coverage, analysis / bioinformatics pipelines and sequencing strategy (targeting / scope), and excluded exons<sup>50</sup>. These data are needed to be able to compare the quality and performance of different providers, and are vital for improving services generally.

There has been a proliferation of genomic databases covering different disease areas, varying in scope, curation, completeness and therefore, clinical utility. Since data deposition to these databases has been voluntary, uptake has been patchy, resulting in fragmented content and poor reliability. As services are scaled up, the absence of a designated genomic database for the NHS, lack of mandated deposition of data, and lack of a robust data sharing strategy within and between NHS-funded genetic testing facilities are likely to be detrimental to providing high quality services. This is an important ethical issue, since promoting both beneficence and non-maleficence are key principles at the heart of healthcare delivery. This is particularly relevant as these technologies are mainstreamed from clinical genetics to other clinical specialties, not least because other specialties may require additional support to utilise these technologies effectively.

## Recommendation 12

**A secure, comprehensive, accessible NHS Database is urgently required that can underpin ongoing genomic sequence interpretation, improve clinical outcomes and support the needs of clinical services. This nationally accessible database should be considered an integral part of NHS genomic testing services and will need to be resourced. Any initiative should be long-term and sustainable.**

Improving the comprehensiveness of any NHS genomic database would improve the clinical utility of the decisions that rely on data in the database, and thus improve the quality of clinical care. However, this might be at the expense of privacy concerns and local ELSI issues. *Mandating* data deposition could be one way of achieving a more comprehensive and robust genomic database, provided that adequate safeguards are in place to protect patient privacy and protect against unauthorised access or data breaches, which could lead to discrimination or stigmatisation.

The consensus amongst workshop participants was that the potential benefits of managed data sharing of genomic information within the NHS to support diagnosis, treatment and care outweigh the potential harms. A strong recommendation to emerge from the project was that all NHS-funded genetic testing facilities **need** to be mandated to share relevant data with other approved laboratories and provided with the appropriate infrastructure and regulatory support to do so. This data should include all variants, phenotypic and clinical information. Aggregating information on variants in patients, as well as clinical data on their symptoms, will support the clarification of associations between variants and disease. Furthermore the sequence data itself can be used to create ethnically matched reference (*i.e.* comparison) genomes, for improving the chances of finding clinically significant variants<sup>51</sup>.

Data deposition seems likely to be achieved through a combination of active data deposition and automated data extraction systems. In Chapter 7, we discuss the rationale for wider data sharing outside the NHS.

*...all NHS-funded genetic testing facilities **need** to be mandated to share relevant data with other approved laboratories and provided with the appropriate infrastructure and regulatory support to do so.*

As the use of genomic sequencing technologies becomes more widespread, the routine sharing of data within NHS systems will enable data about individual variants to be collated. Systems and processes need to be developed to feedback relevant information to those responsible for gene list creation and curation (Chapter 4).

### Recommendation 13

**Deposition of data into the secure NHS Database needs to be (i) mandated through enhanced service specification, accreditation, and commissioning and (ii) supported by NHS England policies. Any compulsory data sharing must be consistent with existing regulatory frameworks, and address potential concerns about safeguarding privacy and identifiability.**

There was wide agreement across Workshops 3-5 that a comprehensive database is needed, but little consensus on whether existing and planned resources (e.g. DECIPHER<sup>52</sup>, LOVD, UK Rare Disease Registration Service, UK Cancer Registration System, the University of Radboud, Nijmegen system, the prospective 100,000 GP database) could provide a model for developing NHS infrastructure and services.

Many genomic databases lack sustained and robust sources of funding, resulting in poor curation and deposition rates. Rather than constructing a new database, it seems sensible to build on existing resources through collaboration: however existing databases might require data to be shared for research or commercial purposes, or with agencies outside the UK, in ways that are inconsistent with the consent given by patients. Significantly, changes to these policies might be outside NHS control.

There are elements to some current databases that could be used as a basis upon which to develop an NHS genomics infrastructure. For illustration, the characteristics of two different systems are summarised in Table 1.

**Table 1 Summary characteristics of different data sharing models**

Characteristic	University of Radboud, Nijmegen, Netherlands	UK Rare Disease Registration Service (in development)
Primary purpose of data sharing	Clinical care and medical research	Clinical care, public health, medical research, commissioning and service provision, patient support, surveillance, outcome monitoring for screening programmes.
What is the source of the data?	Six medical centres and laboratories involved in providing clinical genetics	Multiple data sources from NHS including laboratories, clinics and diagnostic tests; linkage to specialist research registries; data from patient surveys; patient portal. Flexible schema with data items extended to meet user needs
Population served	Four million people within the catchment of the University	England (53.9 million) with potential extension to devolved administrations.
Quality controls	Curation prior to deposition	Curation by registration staff, devolved QA to relevant expert clinical research groups.
Managed or public system?	Managed. Very limited data sharing	Managed system – centrally hosted infrastructure – but federated teams to work with local data providers etc. Data sharing with individual patients through secure portal.

One problem with adapting an existing database is that infrastructure and functionality may be limited; modification or re-purposing is often a complex and difficult process, costing time and money. Developing computational data also requires ongoing investment for analysis and for data storage.

An alternative is to utilise the 100,000 GP infrastructure that will integrate WGS data with clinical phenotypic data – for clinical purposes in addition to the existing research purposes. Current proposals permit non-clinicians to access patient de-identified, but individualised, data behind an NHS firewall. However, the 100,000 GP database will only include WGS data, and it is unknown whether it will have provision for other sequence activity data of clinical use (e.g. targeted tests). One solution might be to dedicate part of the database for collection and collation of genomic data from other tests (including gene list tests and WES) performed in the NHS, with access to that part being limited to NHS personnel. Thus a variety of existing initiatives in the UK and elsewhere could provide a model for the basic infrastructure for an NHS Database.

## Recommendation 14

**The most effective strategy to promoting data sharing will be to build on existing knowledge and systems (both nationally and internationally) and adapt this for the NHS.**

# 7 What should be done?

Chapter 6 explored the minimum pre-requisites for developing an ethical and equitable genomic sequencing service within the NHS. While improving consent processes and data sharing is necessary in order to deliver effective care, it is not sufficient: it is vital that these processes and the infrastructure created are flexible enough to be able to develop as demand increases.

Demand for genomic sequencing will increase over the next decade, as further gene-disease associations are identified, and use of these technologies extend beyond clinical genetics and oncology into other specialties such as cardiology, paediatrics and ophthalmology. Genomic information is also likely to become increasingly accessible as mobile technologies are developed. Once the expanded range of NGS applications become fully integrated into patient care pathways, they are likely to be used in high volume<sup>53</sup>.

In addition to identifying what **needs** to be done, the purpose of this report is to identify what **should** be done to realise the full potential of these technologies. Both are necessary in order to develop policy in an ethical and responsible manner. The *Realising Genomics* project identified three areas requiring concerted policy development:

1. Widening access to the NHS database to researchers and other stakeholders
2. Creating an infrastructure for sharing expertise and for managing the most complex interpretation and disclosure decisions
3. Developing a consistent and responsible approach to reanalysis of sequence data and recontacting patients

*Once the expanded range of NGS applications become fully integrated into patient care pathways, they are likely to be used in high volume.*

## 7.1 Providing wider access to the NHS database to those outside the NHS

The managed access model of data sharing set out in Chapter 6 is an immediate priority for the clinical implementation of new NGS based applications. However, it will be necessary to share patient identifiable data more widely in order to ensure that new knowledge is generated and applied. This will involve sharing data (and possibly samples) with researchers and commercial companies for the purpose of clinical research including drug development and, potentially, non-medical purposes. From a regulatory perspective, it is important that patients are informed that their data may be shared outside the NHS, and that they understand the justification for this. In

the past, secondary researchers have relied on a range of strategies for seeking and securing an explicit or implied consent and for notifying patients when their personal data has been shared with researchers. Distinguishing whether an activity is part of clinical care or research is important here because the context strongly determines the ethical and legal principles that apply.

Some stakeholders report that they sometimes find it difficult to distinguish between research and clinical activities. Clarifying whether a VUS is associated with disease and using population data to exclude suspected disease associated variants is a core clinical activity, but this may also be done in a research setting. The impact of genomics on the boundary between these two settings was the focus for Workshop 2, which concluded that this boundary is sometimes permeable and ambiguous, particularly for patients who may regard research activities as an extension of their clinical care<sup>54</sup>. The main recommendations emerging from this Workshop concerned the need for transparency about the nature of the activity, additional clarity about the obligations of researchers to validate and report pertinent and IFs, and the urgent need for an improved clinical database to assist in genomic sequencing, annotation and interpretation.

Widening the scope and geographical extent of data sharing carries increased risks of breaching individual privacy and confidentiality. These risks depend on what is shared and the extent of linkage to other data sources. A single potentially disease associated variant stripped of name and location data may be effectively anonymised, whereas an individual genome sequence may be more readily identifiable. Similarly, accessing and integrating multiple data types from diverse sources raises increased privacy risks<sup>55</sup>. Data deposition on a public database may raise considerably more concerns than on a managed database. Protections that could be put in place for a managed database include: restricting access to specific groups (such as those involved in delivering patient care, or within a specific organisation such as the NHS), de-identifying sensitive data, or requiring those accessing the database to sign data access agreements including confidentiality statements with sanctions. The UK Biobank provides a good example of data controls in a managed database ([www.ukbiobank.ac.uk](http://www.ukbiobank.ac.uk)).

Ensuring an understanding of the risks and benefits of data sharing (e.g. that the data could enable a diagnosis to be made, help to build a robust evidence base and contribute to treatment development, but also that it may be used more widely, for research, insurance or commercially and could lead to stigmatisation or discrimination) is an important aspect of the consent process. These recommendations are addressed in Chapter 6.

If the NHS database described in Chapter 6 is used for purposes not related to the clinical care of the patient, there must be an appropriate legal basis enabling the processing of the data – which would be ‘sensitive personal data’ under the current UK Data Protection Act (‘the Act’). Under the Act, sensitive personal data can be processed for ‘medical purposes’. ‘Medical purposes’ includes medical diagnosis, the provision of care and treatment, and medical research (Data Protection Act 1998, Schedule 3 Paragraph 8(2)). This means that the data held in the database could be processed for non-clinical purposes if the processing constitutes medical research as long as other relevant data protection criteria are met (the database is secure, the processing is undertaken in a confidential manner *etc.*).



However, this situation could change if future legislation, such as the EU General Data Protection Regulation (GDPR), were to be enacted<sup>56</sup>. In its current form, the GDPR could restrict the scope of existing data-sharing for medical research in the absence of explicit, specific and informed consent; consent for processing would be 'purpose limited'. In order to guard against this possibility and pre-emptively provide for an alternative legal ground for data processing we recommend that consent is explicitly sought from every NHS patient for the processing of personal identifiable data outside clinical care.

Data may be shared outside clinical care for a variety of different purposes, including for the provision of non-NHS healthcare, medical research and for non-medical purposes. The justifications for each of these uses, and the safeguards that need to be put in place will be very different. Any safeguards should comply with legislation and regulation on data protection, but also with the common law of confidentiality, and the infrastructure for ethical and legal scrutiny by Caldicott Guardians. The use of health-related data, for purposes other than clinical care is controversial, and part of a wider debate about the legitimate collection of and access to personal data. In essence, the debate is about balancing the autonomy of the individual against other interests such as: population health, private profit and the autonomy of others. Limitations of space preclude a full exploration of the mechanisms that might be used to balance these different interests, but it should be noted that the collective gains are not necessarily equivalent to the collective losses.

Ultimately, the determination of which interests prevail, and in what circumstances data sharing should be permitted is fundamentally a political decision. However, what is clear is that more effort is needed to make explicit to patients and the public the nature of the compromises and choices required in the implementation of data-heavy projects, particularly in healthcare. This is the case particularly where patient data will be accessed for commercial use, given the sensitivities involved<sup>57</sup>. Delays to the care.data project, for example, are a salutary reminder of how a failure to explicitly debate and address different interests can result in a situation that ultimately serves no-one's interests.

## Recommendation 15

**Systems and legal processes need to be put in place to allow the contents of the NHS Database to be shared more widely outside the NHS. In order to address proposed legislative changes, the optimal method of establishing a firm legal basis for sharing identifiable patient data beyond the clinical care of the patient would be to seek routine appropriate consent. This will contribute to building public trust.**

## 7.2 Mechanisms to facilitate the interpretation of VUS and the disclosure of IFs

Interpreting VUS and determining the 'relevance' of IFs is one of the main challenges of implementing sequencing in clinical practice. The NHS does not have scalable systems in place to deal with interpretation of VUS or the disclosure of IFs.



We recommend that national-level mechanisms be established to help manage these challenges: mechanisms to develop core gene lists (Chapter 4), standards for laboratories regarding when to report IFs to a referring clinician and advice for clinicians as to when and how to disclose IFs to their patient.

### 7.2.1 VUS interpretation

We recommend that an NHS-wide mechanism for sharing VUS data between scientists and clinicians should be used to facilitate VUS identification. This should be enabled by a bottom-up (*i.e.* laboratory-level) alert system built into the data sharing mechanism (Section 6.1.3). Relevant professional bodies should work together to lead policy development in this area.

## Recommendation 16

**A NHS-wide data sharing mechanism should be established to help facilitate VUS interpretation.**

### 7.2.2 Incidental findings

Mandatory standards on when laboratories should report IFs to clinicians should be developed by a national multidisciplinary group. This group should also produce advice to clinicians on when and how IFs should be disclosed to patients.

The multidisciplinary group should include:

1. Relevant medical sub-specialties
2. Laboratory scientists including those with expertise in bioinformatics
3. Clinical geneticists
4. Relevant academics
5. Genetic counsellors
6. Patient organisation representatives

## Recommendation 17

**A national-level multidisciplinary committee should be established to develop standards for laboratories as to when to report VUS and IFs to referring clinicians. This body should also develop advice for clinicians as to whether and how to disclose IFs to patients.**

*Mandatory standards on when laboratories should report IFs to clinicians should be developed by a national multidisciplinary group. This group should also produce advice to clinicians on when and how IFs should be disclosed to patients.*

### 7.3 Reanalysis, recontact and the ongoing duty of care

One advantage of NGS is that sequence data can be reanalysed and reinterpreted if and when new clinical questions are raised and in response to new knowledge. Reanalysis involves reinterpretation of genes that formed part of the original test, or extension to other genes for which data is now available, but for which no analysis or interpretation was originally undertaken. This is done through changing bioinformatics filters to include identification of new known disease associated variants. Currently, there is no obligation to reanalyse sequence data on a systematic basis, although *ad hoc* resequencing does take place. This process might be triggered as a result of new genetic variants being identified and facilitated through increased use of automated bioinformatics pipelines making the process easier and cheaper. Since reanalysis is undertaken on the basis that it might generate clinically actionable findings, this may necessitate recontact with the patient<sup>19</sup>. Alternatively the process of reanalysis could be initiated by a patient enquiry. In either case, this could potentially be time consuming, and raises questions about the duties of the clinician to reanalyse and reinterpret existing clinical data and to recontact the patient<sup>58</sup>.

Reanalysing sequence data in response to new knowledge could generate potential health gains, but this should be balanced with the economic and opportunity costs involved, for example, increased staffing costs and reduced time for new patient consultations. Since reanalysis and reinterpretation are not part of current practice, introducing these on a routine basis, might change the legal standards applied to healthcare professionals (by shifting the duty of care). This could have implications for healthcare practice in other specialties.

There was overwhelming consensus in Workshop 5 that reanalysis and recontact could be beneficial for patients, laboratories and clinicians. If adopted the following details should be included in the initial consent: the likelihood of future reinterpretation and recontact, the time period over which this could occur and how reanalysis and recontact will be initiated as well as the option for the patient to opt out of reanalysis and recontact (Recommendation 10).

Cost is a major barrier to reanalysis and recontact, and these services will only be justified if they offer increased clinical utility or are cost neutral or can be done at marginal cost. Adopting more restrictive approaches, such as reviewing patients when there is new information about pertinent genetic variants or an emerging clinical need, could mitigate increased costs.

#### Recommendation 18:

**A systematic, evidenced-based approach should be taken to reanalysis and recontact. Standardised approaches should be developed through professional standards and guidelines.**

# 8 Technologies in transition - high level infrastructure and future policy development

Chapters 4-7 have addressed the challenge of incorporating genomic sequencing into existing clinical practice and patient pathways and developing the infrastructure for sequencing, annotation and interpretation supported by an evidence base with additional expertise supplied by national multidisciplinary groups.

This chapter explores some of the wider infrastructure and support that should be put in place to enable these systems to work effectively. Some of these issues concern how policies are developed (system development and future proofing). Others reflect specific requirements for support, funding and public engagement that are necessary for these systems and infrastructures to operate efficiently. An additional set of issues concern the wider infrastructure within which health services are managed and delivered: harmonising the quality of tests from different providers through accreditation and quality standards, using these systems of accreditation to ensure equitable access to services (tying in accreditation with commissioning) and determining how these services are funded.

## 8.1 System development

### 8.1.1 Responding quickly and responsibly to new knowledge

As uptake of these technologies increases, there needs to be a sustained effort to gather and evaluate evidence of their impact through continuing ethical, legal and social science research and evaluation. This should help to establish the development of an evidence base, guide clinical implementation, and also help to guide models of good practice in the ethics and governance of genomics at the clinical-research interface. Experience gained through the 100,000 GP is likely to be relevant to this process.

### Recommendation 19

**Ongoing ethical, legal and social science research and evaluation are needed to inform good practice, especially in areas where genomic sequencing technologies raise novel challenges: these include reanalysis, recontact, and the evaluation and reporting of findings.**

WES or WGS, combined with targeted interpretation using gene lists guided by the patient phenotype, can allow diagnostic reanalysis of sequence data as new gene / phenotype associations are discovered. Increased flexibility is achieved through being able to add genes (or remove them) from gene lists (Chapter 4, p24). Using a standardised workflow also results in economies of scale through batching samples. Sequencing costs are therefore likely to become more affordable, particularly if reagent costs continue to decline, although the interpretation costs may continue to be high.

In addition to demonstrating that particular applications have clinical utility, new applications of genomic sequencing must be cost-efficient and cost-effective.

## Recommendation 20

**Urgent health economics analysis is required to demonstrate the circumstances in which genomic sequencing may be more cost-effective than competing technologies. This information may assist in prioritising how genomic sequencing is rolled out across clinical specialities.**

Many genomic databases lack sustained, robust sources of funding. This may result in insufficient curation, leading to those generating genomic data being less willing to deposit data, or clean data for deposition. Sustainable methods of funding an NHS genomic testing database must be developed: these could include subscription or a levy on each genomic test performed, regardless of referral route. Other options might be to require that fees are paid where data is shared outside the NHS, and also where commercial rights, including intellectual property rights, are developed from this data.

## 8.2 Ensuring future sustainability

The pace of change of genomic knowledge means that systems and processes will need to be flexible and accommodating. It is likely that a range of providers, including the commercial sector, will provide parts of the sequencing, annotation and interpretation pipeline. There is debate about the utility of WGS as compared to WES. Whilst WGS offers better quality data than WES (particularly for structural and copy number variation), the sequencing costs of the former are approximately triple those of the latter, and there are significant additional interpretation and downstream costs<sup>37</sup>. However, if sequencing and interpretation costs decline sufficiently, it seems feasible that WGS will become the technology of choice. It is imperative that data systems are developed that have sufficient capacity, because WGS requires far larger and more complex IT resources. Although it might be difficult to future proof systems and processes to ensure that these are platform agnostic, it is vital that providers are able to access sufficient resources to be able to adapt existing processes.

## Recommendation 21

**Systems and processes should be sufficiently dynamic and flexible to be able to respond to future developments, such as the need for increased IT infrastructure and storage as a result of a transition to routine WGS.**

### 8.3 Support for users and mainstreaming

One of the most challenging aspects of realising genomics in clinical practice is to ensure healthcare professionals who utilise these technologies are adequately supported so they may make effective referrals, and can understand the results generated by testing. While consenting people for genetic testing and managing the disclosure of genetic test results are established aspects of the clinical genetics' workload, these activities may be much less familiar to those working in other clinical specialities.

The issue of who should be responsible for ordering genetic tests generated heated debate in Workshop 5. Some participants felt that clinical geneticists had proven experience of these technologies and argued that they should be regarded as the ultimate source of expertise; others felt that other specialties should be free to develop their own guidance on the use of NGS applications, in the knowledge that clinical genetics support was available if needed.

One possibility might be to develop a form of accreditation for those in non-genetic medical specialities who demonstrate sufficient knowledge and have the core competences to be able to order and interpret genomic sequencing tests. Those who are accredited to offer genetic / genomic-testing would be required to demonstrate minimum standards for phenotype collection and a minimum degree of understanding of the results of testing. It was suggested that this accreditation of core competences could be developed by the relevant professional organisations, Royal Colleges and educational establishments with support from, the Joint Committee on Genomics in Medicine, the British Society for Genetic Medicine and other stakeholder groups, in particular Health Education England (HEE). HEE is developing a range of genomics education programmes, at a variety of levels that can be accessed by NHS staff. These range from new Masters level courses in genomic medicine, due to start in 2015, to higher specialist scientific training in bioinformatics and a range of continuing professional development courses for NHS staff in genomic medicine and also in bioinformatics. Further details on HEE's plans for supporting the NHS workforce to deliver genomics are available at [www.genomicseducation.org.uk](http://www.genomicseducation.org.uk).

In some laboratories the majority of genetic tests are ordered by non-geneticists<sup>59</sup>. As the number of non-geneticists ordering NGS tests may well increase, it will be important to ensure that NGS gene panels, WES and WGS reports are straightforward to interpret. Laboratory reports will need to indicate where and when clinical genetics support is likely to be necessary and how it may be accessed.

#### Recommendation 22

**Regardless of clinical specialty, all clinicians requesting diagnostic tests that utilise NGS sequencing will require support in order to deliver a safe and effective service for their patients. Developing core competences for ordering genomic testing should be explored: competences will need to encompass appropriate referral, consent processes and the interpretation of results.**

*One of the most challenging aspects of realising genomics in clinical practice is to ensure healthcare professionals who utilise these technologies are adequately supported so they may make effective referrals, and can understand the results generated by testing.*

## 8.4 Building accountability and transparency

The pace of change, use of commercial providers, and increasing reliance on automated systems to deliver sequencing, annotation and interpretation seems likely to generate concerns about safeguarding the quality and effectiveness of the diagnostic pathway. In the event of multiple providers being involved in the diagnostic pathway, the overall quality and safety of the testing service will need to be assured. In order to safeguard high quality services, and ensure public trust in the systems and processes that are being developed, there will need to be transparency about service specifications, delivery mechanisms and potential conflicts of interests, in order that providers are seen to be accountable for their performance.

### Recommendation 23

**Public confidence is a vital element in securing the successful clinical implementation of novel technologies: it is therefore vital that claims made about their impact are realistic and that services are implemented in ways that are transparent and accountable.**

## 8.5 Securing harmonised genome sequencing and interpretation quality through accreditation

As clinical sequencing becomes more widely used, it is possible that there could be a proliferation and fragmentation of providers, each delivering a small component of the sequencing, annotation and interpretation processes for different healthcare providers. In order to ensure that services are delivered to a consistently high standard, service level specifications should be agreed. In addition, laboratories need to comply with appropriate accreditation standards. Within Europe, there is a voluntary process of validation and verification which records compliance with relevant laboratory standards (such as ISO 15189) and professional guidance<sup>60</sup>. The United Kingdom Accreditation Service is responsible for molecular genetics laboratory accreditation and additional external quality assessment for molecular genetics laboratories is available via the molecular laboratory National External Quality Assessment Service.

The incorporation of genetic and genomic tests within the scope of the revised EU *In Vitro* Diagnostic Devices Regulation will mean that genetic / genomic tests will need formal development and accreditation in the future. This is likely to put pressure on existing national systems, as increased capacity will be needed for validating and accrediting genetic tests.

The UKGTN evaluates genetic tests for rare disorders provided by member laboratories for use in the NHS. New genetic tests using NGS gene panels / WES / WGS methodologies will need to be evaluated to provide evidence of scientific and clinical validity and utility. The evaluation of these technologies is more complex and may require extra resources if lengthy delays in their implementation are to be avoided. Systems to streamline approval of minor changes to gene lists have been developed by the UKGTN: these are necessary to ensure that the UKGTN evaluation system continues to function effectively. If expert groups are convened for gene list construction and curation they could be used to provide expert evidence as part of the evaluation process.

## Recommendation 24

**Systems for evaluating genetic and genome-based tests for use within the NHS need to be supported and developed further to enable timely and robust assessment. Standard operating procedures should be used to manage modest changes to sequencing and interpretation pipelines, and to the contents of gene lists.**

### 8.6 Streamlining test evaluation and funding

Once genetic tests have been evaluated and assessed as having sufficient clinical utility they need to be considered in a timely manner by commissioning bodies. The key challenge is the funding of these technologies. There is evidence from the UKGTN that many new genetic tests are cost-effective, in the sense that the economic gains made in terms of diagnosis outweigh the costs of implementation. However, these cost savings are rarely realised in molecular genetic laboratory budgets but rather across the patient pathway and are therefore more difficult to implement. Commissioning bodies will need to consider the care pathway approach across the health system, otherwise the benefits (including financial) of new genomic technologies will not be realised.

## Recommendation 25

**There needs to be an appropriate commissioning mechanism to consider the implementation and funding of genomic sequencing tests in a timely manner in response to evidence of their clinical utility. This will need to include arrangements for prioritising and managing access to testing, interpretation and follow-up.**

*Commissioning bodies will need to consider the care pathway approach across the health system, otherwise the benefits (including financial) of new genomic technologies will not be realised.*



# Recommendations

## Recommendation 1

The NHS should adopt targeted analysis using gene lists following genome-based sequencing as an assay. This targeted approach will have greater clinical utility for the majority of clinical applications than approaches involving analysis and interpretation of the whole exome or genome.

## Recommendation 2

Use of genomic tests should be justified on a per-test basis, supported by clear, transparent and standardised referral criteria.

## Recommendation 3

Where clinically applicable, we recommend that NGS gene lists incorporating a core / standardised set of genes appropriate to the phenotype are routinely adopted.

## Recommendation 4

(A) Standardised evidence criteria should be developed for the selection and evaluation of genes in gene lists.

(B) Once these are agreed, mechanisms need to be developed for relevant experts in specified clinical areas 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 healthcare professionals and NHS scientists). These activities will need to be resourced.

## Recommendation 5

Bioinformatics search strategies should minimise the generation, interpretation and disclosure of IFs which are outside the scope of the clinical enquiry. This is on the basis that without sufficient evidence for the clinical utility of opportunistic screening, the potential harms are likely to outweigh the potential benefits.

## Recommendation 6

Clinical criteria should be developed for moving from targeted sequencing and analysis to using open sequencing and analysis as a second-line test. Clinical guidelines should also be developed for the use of open sequencing (exome- or genome-based) as a first-line test.

## Recommendation 7

It is the responsibility of the referring clinician to provide transparent information and to seek consent relating to targeted and open sequencing and analysis. This should include advising patients about the possible generation and significance of IFs and VUS, and establishing their views regarding recontact.

## Recommendation 8

The clinical consent process should include an explanation that IFs and VUS may be generated during genomic sequencing, that these may require further investigation, and that the test results may have implications for the patient's biological relatives.



## Recommendation 9

As part of the consent process, patients should be given the opportunity to express their views as to whether IFs generated from genomic sequencing should be disclosed to them. Where appropriate this might form part of a dialogue with clinicians. Disclosure decisions will be informed by clinical judgement.

## Recommendation 10

The possibility and nature of reanalysis necessitating future contact should be routinely covered in the initial consent process if this is part of the testing service (and if necessary supplemented by further discussions). Patients should be given the opportunity to opt-out of recontact. There should be transparency about what findings might be returned, how long after the initial episode of care contact might be made, who would contact the patient and likelihood of this arising, and how the patient may initiate contact.

## Recommendation 11

There must be transparency within the consent process regarding how sequence data are used. We recommend that the initial consenting process is clear that data will be routinely shared within the NHS.

## Recommendation 12

A secure, comprehensive, accessible NHS Database is urgently required that can underpin ongoing genomic sequence interpretation, improve clinical outcomes and support the needs of clinical services. This nationally accessible database should be considered an integral part of NHS genomic testing services and will need to be resourced. Any initiative should be long-term and sustainable.

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The most effective strategy to promoting data sharing will be to build on existing knowledge and systems (both nationally and internationally) and adapt this for the NHS.

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Systems and legal processes need to be put in place to allow the contents of the NHS Database to be shared more widely outside the NHS. In order to address proposed legislative changes, the optimal method of establishing a firm legal basis for sharing identifiable patient data beyond the clinical care of the patient would be to seek routine appropriate consent. This will contribute to building public trust.

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## **Recommendation 18**

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Ongoing ethical, legal and social science research and evaluation are needed to inform good practice, especially in areas where genomic sequencing technologies raise novel challenges: these include reanalysis, recontact, and the evaluation and reporting of findings.

## **Recommendation 20**

Urgent health economics analysis is required to demonstrate the circumstances in which genomic sequencing may be more cost-effective than competing technologies. This information may assist in prioritising how genomic sequencing is rolled out across clinical specialities.

## **Recommendation 21**

Systems and processes should be sufficiently dynamic and flexible to be able to respond to future developments, such as the need for increased IT infrastructure and storage as a result of a transition to routine WGS.

## **Recommendation 22**

Regardless of clinical specialty, all clinicians requesting diagnostic tests that utilise NGS sequencing will require support in order to deliver a safe and effective service for their patients. Developing core competences for ordering genomic testing should be explored: competences will need to encompass appropriate referral, consent processes and the interpretation of results.

## **Recommendation 23**

Public confidence is a vital element in securing the successful clinical implementation of novel technologies: it is therefore vital that claims made about their impact are realistic and that services are implemented in ways that are transparent and accountable.

## **Recommendation 24**

Systems for evaluating genetic and genome-based tests for use within the NHS need to be supported and developed further to enable timely and robust assessment. Standard operating procedures should be used to manage modest changes to sequencing and interpretation pipelines, and to the contents of gene lists.

## **Recommendation 25**

There needs to be an appropriate commissioning mechanism to consider the implementation and funding of genomic sequencing tests in a timely manner in response to evidence of their clinical utility. This will need to include arrangements for prioritising and managing access to testing, interpretation and follow-up.

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# Appendix 1: Glossary

<b>Assay</b>	The process of analysing a physical sample to determine its composition
<b>Cost-effective</b>	Economical in terms of the goods or services received for the money spent
<b>Cytogenetics</b>	The analysis of the number and structure of chromosomes, including copy number variants
<b>De Novo</b>	An alteration in a gene that is present for the first time in one family member as a result of a mutation in a germ cell (egg or sperm) of one of the parents or in the fertilised egg itself
<b>Diploid</b>	The normal number of chromosomes in a somatic cell; in humans, 46 chromosomes (22 pairs of autosomes and two sex chromosomes)
<b>Exome</b>	All the exons in the genome (around 1-2% of the human genome)
<b>Exon</b>	The region of the gene that codes for protein
<b>False positive</b>	A test result which indicates that an individual is affected by a condition or has a certain gene mutation when he or she is actually unaffected or does not have the mutation; <i>i.e.</i> a positive test result in a truly unaffected individual
<b>False negative</b>	A test result which indicates that an individual is unaffected by a condition or does not have a particular gene mutation when he or she is actually affected or does have a gene mutation; <i>i.e.</i> a negative test result in an affected individual
<b>FISH</b>	Fluorescence <i>in situ</i> hybridisation is a laboratory technique for detecting and locating a specific DNA sequence on a chromosome. The technique relies on exposing chromosomes to a small DNA sequence called a probe that has a fluorescent molecule attached to it. The probe sequence binds to its corresponding sequence on the chromosome
<b>Gene list</b>	A collection of genes that relate to a particular phenotype
<b>Genome</b>	The entire genetic material of an organism
<b>Genotype</b>	Specific genetic constitution of an individual
<b>Germline</b>	The sex cells (sperm and egg) which transmit genetic information from one generation to the next
<b>Incidental finding</b>	Disease associated or likely disease associated findings that are not apparently relevant to a diagnostic indication for which the sequencing test was ordered
<b>In silico</b>	Performed on a computer or via computer simulation
<b>Karyotype</b>	The number and visual appearance of the chromosomes in the cell nuclei of an organism
<b>Microarray</b>	An orderly arrangement of thousands of identified sequenced genes printed on an impermeable solid support, usually glass, silicon chips or nylon membrane. Each identified sequenced gene corresponds to a fragment of genomic DNA, cDNAs, PCR products or chemically synthesised oligonucleotides and represents a single gene. Complementary sequences of DNA can be used to hybridise immobilised DNA molecules



<b>Monogenic</b>	Involving or controlled by a single gene
<b>Mutation</b>	Relatively rare change in the DNA sequence from the normal sequence
<b>Next Generation</b>	The collective term for post sanger sequencing that is high throughput and involves massively parallel DNA sequencing
<b>Nucleotide</b>	Molecular unit from which DNA is made, consisting of a nucleobase: adenine (A), guanine (G), cytosine (C), or thymine (T), a sugar molecule and one to three phosphate groups
<b>Open Sequencing</b>	Sequencing the entire exome or genome rather than the subset of genes
<b>Polymerase Chain Reaction</b>	Molecular biology technique in which a fragment of DNA with a specific sequence is copied or amplified exponentially
<b>Phenotype</b>	The observable traits of an organism
<b>Pleiotropic</b>	Where one gene influences multiple seemingly unrelated phenotypic traits
<b>Polymorphism</b>	Common variation in a region of DNA sequence
<b>Sanger sequencing</b>	First generation sequencing which sequences DNA by synthesis using DNA polymerase and involves chain termination
<b>Sensitivity</b>	Statistical measure of the proportion of true positives which are correctly identified <i>i.e.</i> the ability of a test to correctly identify those with the disease
<b>Specificity</b>	Statistical term for the proportion of negatives that are correctly identified <i>i.e.</i> the ability of a test to identify those without the disease
<b>SNV</b>	Single nucleotide variant; changes in a single base at a particular position in the genome
<b>Variants of unknown significance</b>	Genomic variants whose disease-causing potential is unknown

# Appendix 2: Acronyms

ACGS	Association of Clinical Genetic Scientists
ACMG	American College of Medical Genetics and Genomics
BSGM	British Society for Genetic Medicine
CMGS	Clinical Molecular Genetics Society
DDD	Deciphering Developmental Disorders
DECIPHER	Database of Genomic variants and Phenotype in Humans Using Ensembl Resources
DRIP	Data Retention and Investigatory Powers
ELSI	Ethical, legal and social issues
FISH	Fluorescence <i>in situ</i> hybridisation
GOSH	Great Ormond Street Hospital
IF	Incidental finding
JCGM	Joint Committee on Genomics in Medicine
LOVD	Leiden Open Variation Database
NGS	Next generation sequencing
OMIM	Online Mendelian Inheritance in Man
PCR	Polymerase chain reaction
SNV	Single nucleotide variant
UKGTN	UK Genetic Testing Network
VUS	Variant of unknown significance
WES	Whole exome sequencing
WGS	Whole genome sequencing
100,000 GP	100,000 Genomes Project

# Appendix 3: *Realising Genomics*

## project objectives

1. To scope and review existing and emerging use of NGS and WGS and, in particular, how genomic information is conceptualised, managed and used in clinical practice
2. With these developments in mind, to keep appraised of major projects within the UK, such as the 100,000 Genomes Project, and to try to ensure that the objectives, processes and outputs of the *Realising Genomics* project take account of these developments
3. To review the ethical basis upon which novel genomic sequencing technologies are likely to be introduced and used within the NHS, in particular including the factors which differentiate NGS / WGS use in research and clinical settings, and the factors which flow from this distinction
4. To identify and explore key ethical, legal and social questions arising particularly in respect of genomic information, and its categorisation into different classes of findings (e.g. 'incidental' or 'unsolicited' findings)
5. With these issues in mind, to facilitate engagement with stakeholders (e.g. healthcare professionals, laboratory scientists, regulators, policy-makers, patient representatives and lay publics) about how genomic technologies can be implemented to best effect
6. To identify what the implications might be for these stakeholders. This might include educational and training needs, relevant policy development issues and implications for the commissioning process
7. To explore professional and patient experiences and views of the ethical, legal, and social implications of the use of NGS technologies for medical diagnosis and prediction (including their downstream practical implications)
8. To explore practical and conceptual issues described above through reviewing patient pathways in various clinical settings, focusing upon issues around information provision, consent, data sharing and return of results, to include, if applicable, a broader examination of how the role of the patient might change with the implementation of these technologies
9. To identify the key issues that need to be resolved to enable genomic technologies to be implemented to best effect
10. To agree recommendations on how the ethical, legal and social issues relating to genomic information and the use of NGS technologies are best resolved
11. To advise on appropriate guidelines relating to genomic information, and the use of NGS technologies

# Appendix 4: Scientific appendix

## Background

1. Advances in genomic sequencing using NGS technologies have enabled multi-gene sequencing lists to be launched with the aim of testing all of the genes relevant to a patients' condition in a single test, simplifying test selection and referral. Depending on the application, these tests target interpretation according to phenotype to a subset of genes within the list. The ability to group diverse genes into a single test is important where the spectrum of clinical presentations for a particular condition is broad or where a variety of genes may be responsible for a particular phenotype: it also allows for rare genes to be included which non-experts might not identify as immediately relevant<sup>34</sup>. Broad NGS gene lists are being developed containing sets of genes that can be used for testing multiple phenotypes. The development of a clinical exome offers targeting and testing for the full complement of known disease-causing genes (*i.e.* between 2100 and 3500 genes depending upon data source, including GeneTests and Online Mendelian Inheritance in Man (OMIM))<sup>61</sup>. Many centres are exploring using a clinical exome kit as a universal assay and then through bioinformatics filtering, limiting interpretation to those genes that are relevant to the patient's phenotype<sup>34</sup>.
2. The development of NGS platforms that allow the simultaneous massively parallel sequencing of millions of target DNA molecules has significantly reduced the cost and time taken for sequencing compared to pre-existing technologies such as Sanger sequencing. However, the read lengths generated from NGS are substantially lower compared to Sanger sequencing, resulting in the need to reconstruct the genome *in silico* from a much greater number of short fragments of DNA. Most NGS platforms also require the DNA fragments to be amplified prior to sequencing, to ensure they can be reliably measured, which can introduce systematic errors in the sequencing process that are less common with Sanger sequencing<sup>62</sup>. To enable longer continuous read lengths and to reduce errors associated with amplification, many single molecule sequencing methods are currently being developed.

## What is WES or WGS?

3. Where a whole exome or whole genome approach is taken, variants for interpretation are broadened from the restricted set in the gene list. The initial step is that variants that differ from the reference genome are 'called' for further interpretation and analysis. For example, Gilissen *et al* cite a call rate of 0.98 constituting around 3,500,000 single nucleotide substitution variants for WGS and 0.99 constituting around 22,100 single nucleotide substitution variants for exome sequencing<sup>30</sup>. Some variants are called exclusively by either genome or exome sequencing. The variants called exclusively by genome sequencing tend to lie in regions of very low exome coverage whereas the variants called exclusively by exome sequencing tend to lie in regions with very high exome coverage, often caused by mapping issues in repeat regions. As noted in Appendix 5 the genome sequencing process, up to – and including variant call, constitutes the

'assay'. Following variant call, a prioritisation process is used to identify variants of interest for further analysis. This step, and those that follow, constitute the 'test': this element, including the selection of genes for further analysis, will be guided by professional judgement and professional guidance. With open sequencing approaches a full set of known and candidate genes are identified using assumptions about the method of inheritance (*i.e.* diploid and non-diploid to identify somatic and germline mutations respectively). Resulting candidate *de novo* mutations are then interpreted in a systematic manner to ensure that the observed variant is likely to be pathological (through comparison with samples from other family members including parents and unaffected siblings; functional tests; frequency within the population; synonymous and missense mutations). The prioritisation processes vary according to clinical application and the variability of the population presenting with a certain phenotype. Most of the variants will be prioritised through the use of automated bioinformatic pipelines rather than requiring laboratory scientists to sequentially investigate each of the variants identified. With experience the pipelines can be further refined to streamline the process of variant calling.

## What are the advantages and disadvantages of using these tests?

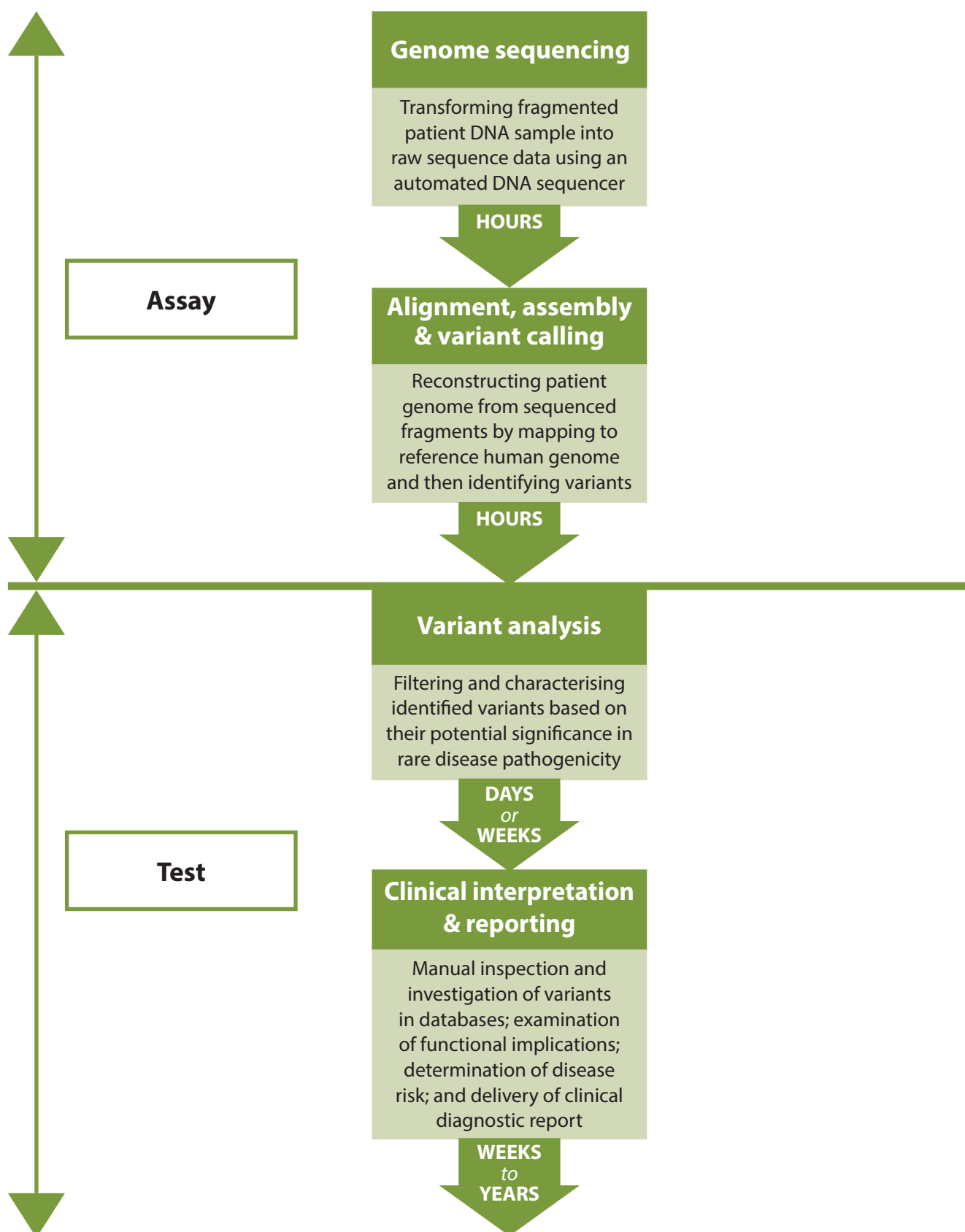
4. Whole exome and genome sequencing and interpretation offer increased coverage of protein coding regions of genes (exons) than targeted tests. Typically WES offers a *theoretical* coverage of 90-95% of the exome but the proportion covered to a clinically useful depth might be lower, between 65-75%. At present, most laboratories supplement disease targeted tests with Sanger sequencing to fill identified gaps in genes denoted as 'core' for that disease. If WES / WGS are used more widely there will be costs associated with the use of Sanger sequencing to validate the variants detected. It should be noted that the ACMG recommend that exome or genomic approaches should be reserved for those cases where negative results have been obtained from disease-targeted testing (including gene lists) or where more targeted testing is less feasible in terms of time or cost-effectiveness. The accuracy of NGS-based diagnostic tests in terms of their sensitivity and specificity raises issues about their clinical utility, and their potential to benefit or harm patients. Using a test that has high false positive or false negative rates may be ethically unsound if alternative tests are more reliable. The choice of NGS diagnostic testing versus alternative testing strategies is addressed in chapters 3 and 4.
5. The probability of identifying VUS and IFs is increased if known and candidate genes are implicated in a variety of different conditions. For example, genes associated with intellectual disability are pleiotropic in that they are also associated with epilepsy and several metabolic disorders. However the protocol for annotation and interpretation may specifically exclude severely disruptive mutations that can be classified as 'not relevant' because they relate to phenotypes that are outside the scope of the clinical question<sup>30</sup>.

## New technologies under development

6. To enable longer continuous read lengths and to reduce errors associated with amplification, many single molecule sequencing methods are currently being developed. The most widely used single-molecule platform currently in use is the PacBio RSII, which employs sequencing by synthesis (the same approach used by short-read NGS platforms) incorporating fluorescent nucleotides into single, isolated molecules of template DNA and employing high resolution video technology to identify the sequence of nucleotide addition as it occurs<sup>63</sup>. The advantage of this approach is that sequencing occurs in real time and does not require amplification. The disadvantages are that sequencing single molecules at a time is a lower throughput approach than that employed by most massively parallel NGS platforms, limiting the volume and depth of analysis, and the equipment is costly and large compared to other bench-top NGS platforms. At present this approach is used principally for sequencing small genomes, such as those of bacteria, or in combination with short read sequencing of larger genomes, where the long reads from the PacBio can be used to close gaps in the genome assembly. Other single molecule methods under development focus on the use of nanopores, which may be biological or inorganic, through which DNA strands or individual bases can pass<sup>64</sup>. Changes in electrical current across the membrane in which the nanopores are embedded are monitored and the sequential passage of different bases through the pore can be identified as each base blocks the current by a different amount. This method can be made massively parallel by having hundreds of nanopores on a chip, each processing a single molecule at a time. Most importantly, such nanoscale sensors can be packaged inside very small, mobile, potentially even disposable devices. Indeed a portable USB connected nanopore sequencer made by Oxford Nanopore Technologies is currently being evaluated by research groups around the world. While these approaches are very promising the need to improve their accuracy, reliability and stability means that they are not yet ready for clinical use.

Disclaimer: This report is accurate as of November 2014, but readers should be aware that genome sequencing technology and applications will continue to develop rapidly from this point.

# Appendix 5: Steps in whole genome analysis



# Appendix 6: Steering group membership

Dr Fiona Cunningham	Ensembl Coordinator & Ensembl Variation Project Leader, EMBL-EBI, Genome Campus, Hinxton, Cambridge
Professor Anneke Lucassen	Professor of Clinical Genetics, Faculty of Medicine and Wessex Clinical Genetics Service, University of Southampton
Dr Anna Middleton	Ethics Researcher and Registered Genetic Counsellor, The Wellcome Genome Campus, Hinxton, Cambridge
Dr Sarah Wynn	Information Officer, Unique
Professor Michael Parker	Professor of Bioethics and Director of the Ethox Centre, Department of Public Health, University of Oxford, Oxford
Dr Christine Patch	Consultant Genetic Counsellor & Reader in Clinical Genetics, Guys & Thomas' NHS Foundation Trust, Guy's Hospital, London
Dr Lucy Raymond	Consultant in Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge, Cambridge
Professor Heather Skirton	Professor of Applied Health Genetics, Faculty of Health, Education and Society, Plymouth University, Plymouth
Dr Jo Whittaker	Senior Fellow and Associate, PHG Foundation, Cambridge
Dr Caroline Wright	Senior Scientific Manager, Wellcome Trust Sanger Institute Wellcome Trust Genome Campus, Hinxton, Cambridge
Dr Jane Kaye	Wellcome Trust Research Fellow, Ethox Institute of Health Studies, University of Oxford, Oxford



# Appendix 7: Workshop delegates

## (workshops attended indicated)

<b>Dr Stephen Abbs</b>	Director of Genetics Laboratories, Medical Genetics, Cambridge University Hospitals NHS Foundation Trust, [WS3,4]
<b>Dr Richard Baird</b>	Academic Consultant in Experimental Cancer Therapeutics, University of Cambridge, Addenbrooke's Hospital, Cambridge [WS2]
<b>Dr Mark Bale</b>	Deputy Director, Health Science & Bioethics Division, Department of Health, London [WS4,5]
<b>Dr Elijah Behr</b>	Senior Lecturer & Honorary Consultant Electrophysiologist, Cardiac & Vascular Division, St George's Hospital, University of London [WS2]
<b>Dr Barbara Biesecker</b>	Associate Investigator, National Human Genome Research Institute / NIH, Bethesda, Maryland, USA [WS1]
<b>Dr Leslie Biesecker</b>	Chief and Senior Investigator, Genetic Disease Research Branch, National Human Genome Research Institute / NIH, Bethesda, Maryland, USA [WS1]
<b>Dr Ruth Charlton</b>	Scientific Director of Molecular Genetics, Leeds Teaching Hospital Trust, St James's University Hospital [WS4]
<b>Dr Victoria Chico</b>	Lecturer in Law, University of Sheffield [WS3,5]
<b>Professor Patrick Chinnery</b>	Director, Institute of Genetic Medicine, Newcastle University [WS2]
<b>Dr Trevor Cole</b>	Consultant in Clinical and Cancer Genetics, Birmingham Women's Hospital NHS Foundation Trust [WS5]
<b>Mrs Buddug Cope</b>	Director of Development, Genetic Alliance UK, London [WS2]
<b>Ms Gill Crawford</b>	Clinical Doctoral Fellow, CELS (Clinical Ethics and Law at Southampton), University of Southampton [WS1]
<b>Professor Nick Cross</b>	Professor of Human Genetics, Faculty of Medicine, University of Southampton [WS4]
<b>Dr Fiona Cunningham</b>	Ensembl Variation Project Leader, European Bioinformatics Institute, Wellcome Trust Genome Campus, Cambridge [WS3]
<b>Dr Ann Dalton</b>	Director, Sheffield Diagnostics & Genetics Service, Sheffield Children's NHS Foundation Trust [WS4,5]
<b>Mr Andrew Devereau</b>	Director, NGRL Manchester, Centre for Genomic Medicine, St Mary's Hospital, Manchester [WS3]
<b>Dr Angela Douglas</b>	Scientific Director, Cheshire & Merseyside Genetics, Liverpool Women's Hospital [WS4,5]
<b>Professor Sian Ellard</b>	Professor of Human Molecular Genetics, University of Exeter Medical School, Royal Devon & Exeter Hospital [WS4]
<b>Dr Catherine Elliott</b>	Director of Clinical Research Interests, Medical Research Council, London [WS2]
<b>Dr Ilse Feenstra</b>	Clinical Geneticist, Radboud University Medical Centre, Nijmegen, The Netherlands [WS4,5]

<b>Dr Helen Firth</b>	Consultant Clinical Geneticist, Cambridge University Hospitals NHS Trust, Medical Genetics, Addenbrooke's Hospital, Cambridge [WS2]
<b>Professor Frances Flinter</b>	Consultant in Clinical Genetics & Caldicott Guardian, Genetics Department, Guy's & St Thomas' NHS Foundation Trust, Guy's Hospital, London [WS2,4]
<b>Dr Tom Fowler</b>	Director of Public Health, Genomics England [WS5]
<b>Dr Christian Gilissen</b>	Researcher in Bioinformatics, Radboud University Medical Centre, Nijmegen, The Netherlands [WS3]
<b>Dr Andrew Grace</b>	Consultant Cardiologist, Papworth Hospital, Cambridge [WS5]
<b>Ms Georgina Hall</b>	Consultant Genetic Counsellor, Manchester Centre for Genomic Medicine, St Mary's Hospital [WS3,5]
<b>Mrs Karen Harrison</b>	Project Manager, Endocrine Awareness Project, ALD Life, London [WS5]
<b>Dr Ari Haukkala</b>	University Lecturer, Department of Social Psychology, University of Helsinki, Finland [WS1]
<b>Mr David Head</b>	Chief Executive, RP Fighting Blindness, Buckingham [WS3]
<b>Dr Lidewij Henneman</b>	Associate Professor, Senior Researcher, Department of Clinical Genetics, Community Genetics, VU University Medical Center, Amsterdam [WS1]
<b>Professor Henry Houlden</b>	Professor of Neurology / Neurogenetics, UCL Institute of Neurology, London [WS3]
<b>Dr Melita Irving</b>	Consultant, Department of Clinical Genetics Guy's & St Thomas' NHS Foundation Trust, Guy's Hospital, London [WS3,5]
<b>Mr Leigh Jackson</b>	Researcher, University of Plymouth, Plymouth [WS1]
<b>Dr Louise Jones</b>	Head of Translational Research, CRUK, London [WS2]
<b>Dr Jane Kaye</b>	Director, HeLEX, Department of Public Health, University of Oxford [WS1]
<b>Dr Dorian Kennedy</b>	Deputy Director of Genetics & Scientific Development, Department of Health, London [WS3]
<b>Mr Alastair Kent</b>	Director, Genetic Alliance UK, London [WS2,5]
<b>Dr Bronwyn Kerr</b>	Consultant Clinical Geneticist, Clinical Genetics Service, Manchester Centre for Genomic Medicine, Central Manchester University Hospitals NHS Foundation Trust [WS4,5]
<b>Dr Abhijit Kulkarni</b>	Head, Microarrays & Molecular Genotyping, South West Thames Regional Genetics Service, St Georges NHS Hospital Trust, London [WS3]
<b>Professor Graeme Laurie</b>	Professor of Medical Jurisprudence, University of Edinburgh [WS2]
<b>Dr Nick Lench</b>	Director, NE Thames Regional Genetics Service, Great Ormond Street Hospital for Children NHS Foundation Trust, London [WS3,4]
<b>Ms Katherine Littler</b>	Senior Policy Adviser, The Wellcome Trust, London [WS2]
<b>Professor Anneke Lucassen</b>	Professor of Clinical Genetics, Faculty of Medicine and Wessex Clinical Genetics Service, University of Southampton [WS2,5]
<b>Dr Dorien Lugtenberg</b>	Clinical Laboratory Geneticist, Radboud University Medical Center, Nijmegen, The Netherlands [WS4,5]

<b>Dr Sheelagh McGuinness</b>	Birmingham Fellow, Centre for Health Law, Science & Policy, Birmingham Law School, University of Birmingham [WS2]
<b>Mr Nick Meade</b>	Policy Analyst, Genetic Alliance UK, London [WS3]
<b>Dr Karen Melham</b>	Senior Researcher in Ethics, HeLEX – Centre for Health, Law and Emerging Technologies, University of Oxford, Oxford [WS5]
<b>Dr Anna Middleton</b>	Ethics Researcher & Registered Genetic Counsellor, The Wellcome Trust Sanger Institute, Genome Campus Hinxton, Cambridge [WS1,3]
<b>Professor Fiona Miller</b>	Associate Professor, Institute of Health Policy, Management & Evaluation, University of Toronto, Ontario, Canada [WS1]
<b>Dr Shehla Mohammed</b>	Consultant Clinical Geneticist and Head of Service, Clinical Genetics, Guy's Hospital, London [WS4]
<b>Dr Kai Ren Ong</b>	Consultant in Clinical and Cancer Genetics, Birmingham Women's NHS Foundation Trust [WS4]
<b>Dr Liz Ormondroyd</b>	Genetic Counsellor / Researcher, Department of Cardiovascular Medicine, University of Oxford [WS3]
<b>Dr Alasdair Parker</b>	Consultant Paediatric Neurologist & Associate Lecturer, Child Development Centre, Addenbrooke's Hospital, Cambridge [WS5]
<b>Professor Michael Parker</b>	Professor of Bioethics and Director of the Ethox Centre, Nuffield Department of Population Health, University of Oxford [WS1,2]
<b>Dr Christine Patch</b>	Consultant Genetic Counsellor, Clinical Genetics, Guys and St Thomas NHS Foundation Trust, Guy's Hospital, London [WS4]
<b>Dr Simon Ramsden</b>	Consultant Clinical Scientist, Manchester Centre for Genomic Medicine, St Mary's Hospital [WS3,4]
<b>Dr Jem Rashbass</b>	National Director for Disease Registration, Public Health England, London [WS5]
<b>Dr Lucy Raymond</b>	Reader in Neurogenetics & Honorary Consultant in Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge [WS3]
<b>Professor Martin Richards</b>	Emeritus Professor, Centre for Family Research, University of Cambridge [WS2]
<b>Ms Laura Riley</b>	Ethics Adviser & Ethics Programme Manager, Genomics England, London [WS2,3,4,5]
<b>Dr Beverly Searle</b>	Chief Executive Officer, Unique – Understanding Chromosome Disorders, Oxted, Surrey [WS3]
<b>Dr Anneke Seller</b>	Consultant Clinical Scientist, Director of Genetics Laboratories, Oxford University Hospitals NHS Trust, The Churchill Hospital [WS3]
<b>Dr Shiri Shkedi-Rafid</b>	Genetic Counsellor & post-doctoral Researcher, Clinical Law & Ethics in University of Southampton (CELS), Princess Anne Hospital [WS2]
<b>Dr Claire Shovlin</b>	Senior Lecturer & Honorary Consultant in Respiratory Medicine, Vascular Science Unit, Imperial College, NHLI, London [WS4]
<b>Professor Heather Skirton</b>	Professor of Applied Health Genetics, Plymouth University [WS3]
<b>Dr Ingrid Slade</b>	Specialty Registrar in Public Health, Oxford University Hospitals, Nuffield Department of Population Health [WS3,5]

<b>Ms Alice Tuff-Lacey</b>	Stratified Medicine Programme Manager, CRUK [WS2]
<b>Dr Susan Wallace</b>	Lecturer in Population & Public Health Sciences, University of Leicester [WS2]
<b>Dr Yvonne Wallis</b>	Principal Clinical Scientist, West Midlands Regional Genetics Laboratory, Birmingham Women's NHS Foundation Trust [WS4]
<b>Dr Diana Wellesley</b>	Consultant in Clinical Genetics, University Hospitals Southampton, Wessex Clinical Genetics Service, Princess Anne Hospital, [WS5]
<b>Mrs Jacquie Westwood</b>	Director, UK Genetic Testing Network, London [WS4]
<b>Dr Simon Woods</b>	Co-Director Policy Ethics & Life Sciences Research Centre & National Research Ethics Advisor, Newcastle University [WS2]
<b>Dr Caroline Wright</b>	DDD Project Manager, Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge [WS5]
<b>Dr Sarah Wynn</b>	Information Officer, Unique [WS2,4]
<b>Dr Ron Zimmern</b>	Chairman, PHG Foundation, Cambridge [WS1,2]

# Appendix 8: Briefing notes

<b>Workshop 1</b>	<b>ELSI* and the implementation of WGS / WES in clinical practice</b>	<b>70-74</b>
<b>Workshop 2</b>	<b>Genomics and the boundary between research and clinical care and treatment</b>	<b>75-78</b>
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# 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.

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 healthcare 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.

## 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 healthcare 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 recontact.

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 healthcare 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 healthcare 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 / healthcare 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.

# 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.

*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.*

- 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.
- 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 different 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.

*There are good reasons for applying different ethical frameworks to research and clinical care.*

## 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.

## 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.

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

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 recontact 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.

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 (March 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.

# 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.

## 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 exome and 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 reanalysis (see panel, left).

## The UK context

Genetic testing for rare diseases is usually accessed through clinical genetics teams which use 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 recontact. A pragmatic approach might be to simultaneously seek consent from patients for various elements: targeted and open approaches and subsequent recontact.

## 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 recontact or reanalysis of inconclusive results vary: patients typically want relevant information especially if actionable, but most delegates felt that recontact 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.

### 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 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.*

## 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.

## 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.

### 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

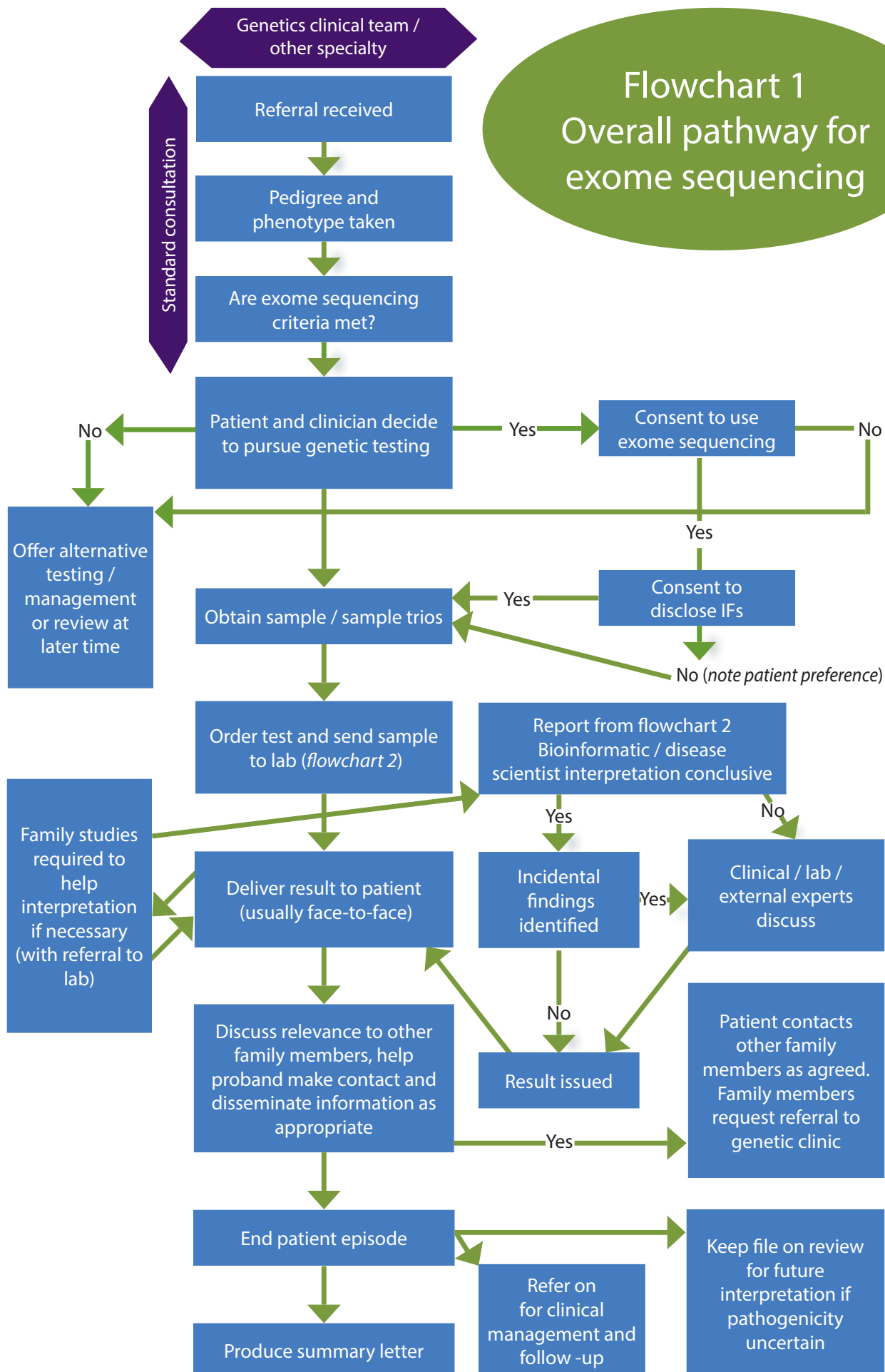
There was support for systematic reanalysis and recontact but significant concerns that the associated cost and workload would be prohibitively high. More work is needed to determine how to operationalise this whilst addressing the ELSI issues that might arise.

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

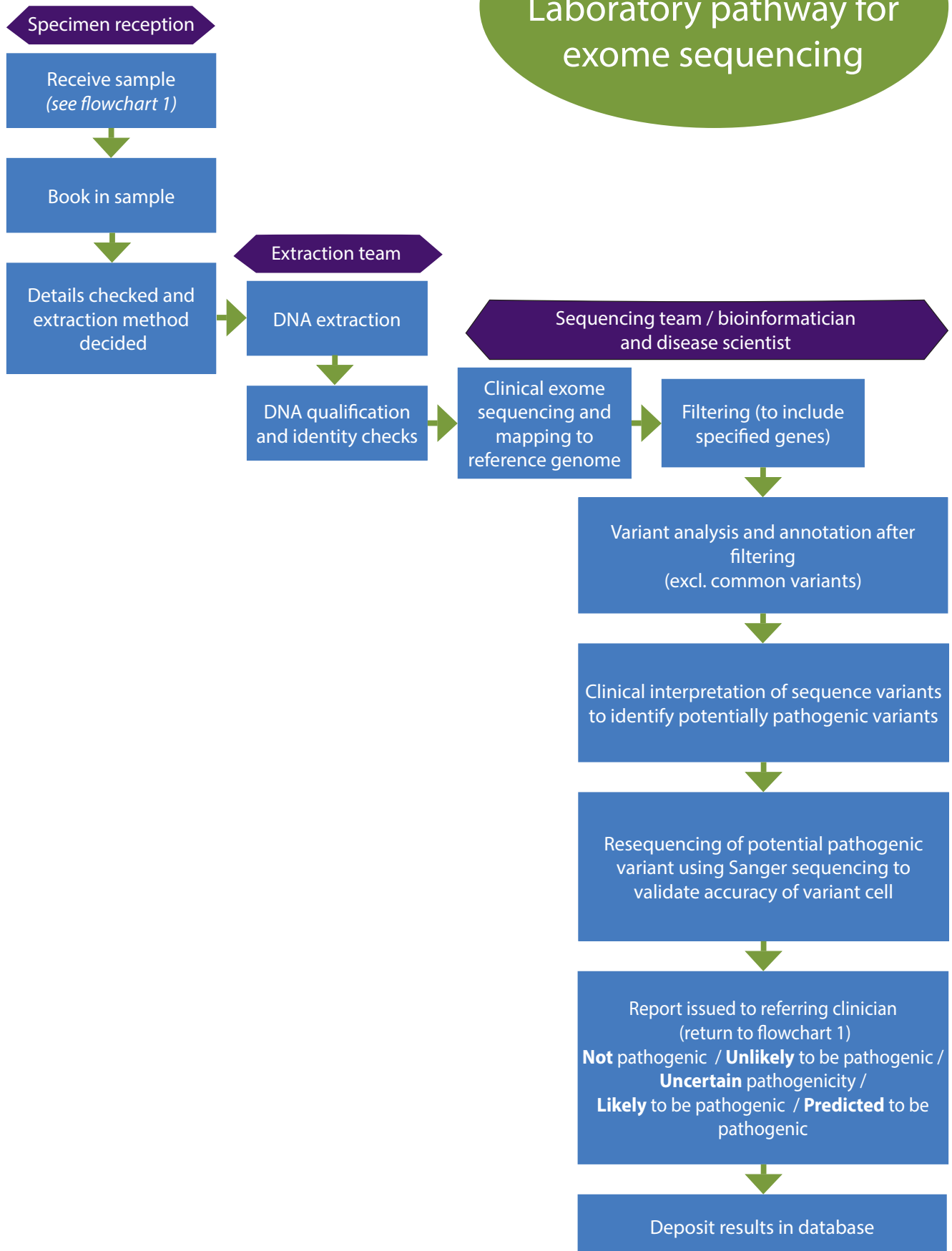
Sequencing and interpretation services seem likely to be secured through a mix of private and public providers. International efforts to agree minimum standards for diagnostic pathways are vital.

# Appendix 9: Diagrams

Flowchart 1	
Overall pathway for exome sequencing	84
Flowchart 2	
Laboratory pathway for exome sequencing	85



## Flowchart 2 Laboratory pathway for exome sequencing





## 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.



978-1-907198-15-1



CAMBRIDGE UNIVERSITY  
Health Partners

Knowledge-based healthcare

PHG Foundation  
2 Worts Causeway  
Cambridge  
CB1 8RN

T +44 (0) 1223 761 900

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

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