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Realising Genomics in Clinical Practice

Executive Summary

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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.

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.

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.

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.

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

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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. 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. 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).

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.

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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.

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