Delivering Genomic Medicine at a Population Level: beyond the 100,000 Genomes Project

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What is Genomic Medicine?

“an emerging medical discipline that involves using genomic information about an individual as part of their clinical care eg for diagnostic or therapeutic decision-making, and the health outcomes and policy implications of that clinical use”

NIH National Human Genome Research Institute
Impact of Genomic Medicine

Earlier Diagnosis
- More precise diagnosis
- More effective treatments
- Fewer adverse reactions
- Eligibility for clinical trials

Greater diagnostic yield
- 60%+ actionable genes in cancer
- 4-5x increase in rare disease

Reduce 'diagnostic odyssey'
- More treatment possibilities with early stage disease

GENOMIC TESTING - supporting precision & personalisation

Inferring predisposition markers
- By better characterisation of condition & driver targets

Prognostics/preventative approaches

Through identification of predisposition to side effects

More precise diagnosis
- Providing clear identification of underlying cause of disease & segmentation of condition

Precise diagnosis allows better treatment selection & increased effectiveness
The NHS & 100,000 Genomes Project: harnessing its unique potential to deliver genomics

NHS "urgently" needs to develop the tools and expertise needed to take advantage of a revolution in genetic testing, June 2011

The 100,000 Genomes Project was announced by the Prime Minister, December 2012

An Olympic Legacy

Genomics England was announced by the Secretary of State for Health at NHS 65th Anniversary Celebrations, July 2013
# 100,000 Genomes Project: establishing the approach for future care

## PRINCIPLES

**100,000** genomes from Rare Disease (families) & Cancer (people & tumours)

4 key principles:
- WGS extends current diagnostic scope
- Recruitment from routine care, treated through routine channels
- Participants consent to sharing of de-identified data for R&D & industry use & for longitudinal access
- Establishes model for transformational change

## INFRASTRUCTURE

13 NHS Genomic Medicine Centres covering populations of **3-7 million**

Networked with **90** NHS hospital organisations (of circa 200) to ensure access – outreach clinics into other NHS orgs & link to other UK countries

Contractual requirements include common protocols, data sharing, collation & submission against agreed data standards & sets

National networking, groups & events to drive standardisation, sharing of best practice & to drive improvements

## LEGACY

4 key legacies:
- Increased discovery of new pathogenic variants
- Integrating advanced genomics into mainstream NHS
- Increasing public understanding & support
- Stimulating and advancing UK life sciences industry

HEE Genomics Education Programme enhances system capacity across the NHS’s **1.3 million staff**

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**GENOMIC MEDICINE - CORE PATHWAY**

- Identification of suitable patients from routine care
- Involvement of patients in ethics, data & consent issues
- Supply of high-quality processed samples
- Collection of linked phenotypic and clinical data
- Validation of WGS findings and feedback to patients
Developing infrastructure: NHS Genomic Medicine Centres

13 new centres delivering NHS contribution to 100,000 Genomes Project:

- Coordinating activity across population areas (>100 independently-managed hospitals & clinics)
- Working in national network to ensure delivery of a standardised national approach – samples & data
- Liaise with national infrastructure overseen by Genomics England (*WGS provision, Clinical Interpretation, National Genomic Database*)
- Overall performance management by national team
North Thames GMC

Bart’s Health

Great Ormond Street

London North West Healthcare

Moorfields Eye Hospital

Royal Free London

Royal National Orthopaedic Hospital

UCLH
North Thames Recruitment

• GMCs on target to meet 60,000 Rare Disease patient sample target by Sept 2018
• NT amongst top 4 GMCs that have recruited nearly half of all patients

• NT is one of 5 Cancer Accelerator Sites
• Recruited almost 70% of all cancer patient samples
### Return of Cancer WGS results

#### Domain 1 Variants

Variants in a virtual panel of potentially actionable genes*. Actionable genes are defined as genes in which small variants (SNVs and indels <50bp) have reported therapeutic, prognostic or clinical trial associations, as defined by the Genomics England Knowledge Management System. Where known, the “variant-level actionability” category and applicable tumour type are indicated. For other variants in these genes, their impact on gene function has not yet been characterised and therefore their actionability status is unclear. This means:

1. Local evaluation will be required for listed variants which are not yet characterised (i.e. “variant-level actionability” is denoted N/A)
2. Even if well characterised as actionable for some tumour types, the listed variants may not be actionable in the participant’s specific tumour type

*Current potentially actionable genes for solid tumours: 77 genes, listed at [Actionable genes in solid tumour v1.0 document](#).

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene-level actionability</th>
<th>GRCh37 coordinates</th>
<th>Transcript</th>
<th>cDNA and protein change</th>
<th>Predicted consequences</th>
<th>Germline 1K Genomes allele frequencies</th>
<th>VAF</th>
<th>All allele/total read depth</th>
<th>COSMIC ID</th>
<th>Variant-level actionability</th>
<th>Gene mode of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>Therapeutic (isolated ca)</td>
<td>12:23398286 C→A</td>
<td>ENST0000029687</td>
<td>c.530G→T p.Gly172Val</td>
<td>missense_variant</td>
<td>N/A</td>
<td>0.28</td>
<td>33/119</td>
<td>COSM529, COSM140133</td>
<td>Therapeutic (isolated ca)</td>
<td>oncogene</td>
</tr>
</tbody>
</table>

#### Domain 2 Variants

Variants in a virtual panel of cancer-related genes**. Cancer-related genes are defined as genes in which any variants have been causally implicated in cancer, as defined by the Cancer Gene Census (Wellcome Trust Sanger Institute).

**Current cancer-related genes: 500 genes, listed at [Cancer census genes v1.0 document](#).

<table>
<thead>
<tr>
<th>Gene</th>
<th>GRCh37 coordinates</th>
<th>Transcript</th>
<th>cDNA and protein change</th>
<th>Predicted consequences</th>
<th>Germline 1K Genomes allele frequencies</th>
<th>VAF</th>
<th>All allele/total read depth</th>
<th>COSMIC ID</th>
<th>Gene mode of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAT1</td>
<td>4:18754186 C→T</td>
<td>ENST00000441802</td>
<td>c.555A→G p.Val195Lys</td>
<td>missense_variant</td>
<td>N/A</td>
<td>0.3</td>
<td>30/101</td>
<td>COSM184196, COSM184194</td>
<td>tumour suppressor</td>
</tr>
<tr>
<td>IDH2</td>
<td>1:50593139 T→C</td>
<td>ENST00000310062</td>
<td>c.316A→G p.Arg105Gly</td>
<td>missense_variant</td>
<td>N/A</td>
<td>0.26</td>
<td>31/118</td>
<td>COSM330311</td>
<td>oncogene</td>
</tr>
</tbody>
</table>

#### Sequencing Quality Information

See online [Technical Information v1.0 manual](#) document and/or LabKey QC portal for details and expected ranges of QC metrics.
Additional Information

Structural variants
Mutational density
Coverage and copy number

Mutational signatures

Mutation context

Signature 1

Cancer types: Signature 1 has been found in all cancer types and in most cancer samples.

Proposed etiology: Signature 1 is the result of an endogenous mutational process initiated by spontaneous deamination of 5-methylcytosine.

Additional mutational features: Signature 1 is associated with small numbers of small insertions and deletions in most tissue types.

Comments: The number of Signature 1 mutations correlates with age of cancer diagnosis.
Clinical utility: actionable information for cancer patients

Early analysis found 65% of Project cancer cases have variants in actionable genes

- WGS provides extra diagnostic reach (structural variants, copy no. variants etc)
- Global patterns of mutation (‘signatures’) proving informative
- Defining causal drivers from benign ‘passengers’ is critical
What the Project has taught us.....

<table>
<thead>
<tr>
<th>Sample type</th>
<th>No. passed QC</th>
<th>No. failed QC dCq + concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germline</td>
<td>1101 (89%)</td>
<td>14 (1%)</td>
</tr>
<tr>
<td>FF</td>
<td>932 (92.46%)</td>
<td>11 (1%)</td>
</tr>
<tr>
<td>FFPE</td>
<td>206 (67%)</td>
<td>76 (30%)</td>
</tr>
<tr>
<td>Total</td>
<td>2239 (88%)</td>
<td>101 (5%)</td>
</tr>
</tbody>
</table>

Formalin damages DNA – WGS full of artifacts
Key developments in cancer

Samples

Tissue handling changes

Tissue samples collected from formalin free theatres

Whole Genome Sequencing

Cancer fast track samples collected & turned around in 20 days

High quality sequencing including mutational signatures & mutational burden

Analysis and Reports

Genomic data returned to NHS GMCs - SNVs, SV, CNVs

65% actionability

Access to clinical trials

Figures as at 22 November 2017
What the Project taught us……..

• **Variability in access to, level and type of genomic testing** across the country especially evident in cancer and in common diseases

• **Variability in quality** of sample handling, processing, assessment and testing performed in cancer

• **Wide variability in the care pathway** and utility of genomic information even if treatment can be targeted

• **Informatics and data infrastructure** needed considerable development
Providing proof of concept for a mainstream genomic medicine service

Proof of concept for routine care established
Feasibility & affordability of WGS demonstrated
Consent & data sharing for multiple purposes demonstrated
Capturing high quality data & samples for multiple purposes
Standardisation of processes, pathways & data flows being embedded
Beginnings of system-wide involvement established
Clinical leadership in place
System planning & commissioning being aligned

Transformed pathways of care based on careful characterisation of patients facilitating tailored interventions

The exemplar cancer pathway

Exemplar pathway captures what has been learnt so far and outlines how effective transformation has been successfully applied to existing care pathways.

How do we apply this learning to the diversity of NHS services & cancer pathways?
NHS Genomic Medicine Service: the vision for the future

The NHS will have:

• A national Genomic Medicine Service providing consistent & equitable care for the country’s 55 million population

• Operating to common national standards, specifications & protocols

• Delivering to a single national testing directory – covering use of all technologies from single gene to whole genome sequencing

• Building a national genomic knowledge base to inform academic & industry research & discovery inc. clinical trials recruitment

Consolidating existing services and approaches to improve access to the best of current NHS practice + preparedness to deliver future technologies as they arise
The national infrastructure for genomic medicine

Political oversight: DHSC & Ministerial Board

NHS Genomic Medicine Service

- Genomic Medicine Centres & Genomic Clinical Services
- National Network of Genomic Laboratories
- National Test Directory

Informatics systems & data store

National Whole Genome Sequencing Provision

Clinical Interpretation

Workforce development

Industry/ academic/ international partnerships

Built on existing provision – developing capacity to deliver future technologies
New national network of genomic laboratories

NHS England are commissioning a future system that will influence, innovate and strategically prioritise the future delivery of genomic & personalised medicine

This includes:

- National network of provision inclusive of cancer genomics
- Delivery of a single uniform national genomic test directory – delivered through standard operating procedures to ensure quality and comparability
- Equitable & consistent access to testing provision
- Up to 7 Genomic Laboratory Hubs aligned to Sustainability & Transformation Partnership areas

Procurement process structured to drive the establishment of a world-class resource for the NHS delivering cutting-edge technology for patient benefit
OVERVIEW

Covers the complete genomic testing spectrum for rare disease and cancer from single gene through to WGS commissioned by the NHS in England. Structured by:

- Clinical Indication
- Test Scope
- Test name
- Technology
- Targets/Genes
- All cancer tests currently listed as core

It will be refreshed annually.

Draft directory published as part of NHS England ITT in December – updated version released early March.

Background Methodology

NHSE evaluated internationally available frameworks for evaluating genomic tests – combined best aspects of these to create bespoke framework relevant to our health system.

NHS England’s policy for evaluating genomic tests in the NHS will be published for consultation shortly.

Work of L Modliano
Wide Consultation

- Co-ordinated by Cancer Transition Working Group
- Consultees included representatives from:
  - National Cancer Research Institute Clinical Studies Groups
  - National Cancer Research Institute Cellular Molecular Pathology Initiative
  - Cancer Programme of Care
  - NHS England (including commissioners)
  - Cancer Leads from the 13 Genomic Medicine Centres
  - Cancer Research UK
  - Leads of each of the Genomics England Clinical Interpretation Partnerships cancer domains
  - Genomics England
- Face-to-face workshop (May 23rd 2017) followed by completion of an online tool
- List of consultees chosen to ensure representation from across tumour types and invited to solicit expert input from chosen members of their respective clinical communities
Future-enabled to keep pace with technological advance

• The Directory will be **updated annually** through a **clear and transparent process**, with specified timelines and governance.

• The process for evaluating genomic tests has three key aims:
  1. To **systematically review** all available genomic testing by condition to inform the definitive repertoire of tests
  2. To **standardise the testing available** by defining the specific genes that need to be tested for and by which technology the testing should be delivered
  3. To support the ongoing evaluation of new tests and technologies to **enable access** to the most effective and affordable technologies now and in the future

• A **committee of clinical and scientific experts** from across the UK will be established to oversee and implement the evaluation process.

• The evaluation process will be set out by **NHS England** later in the year.
Development of a testing strategy

Wave 1
- **Stream Z**
  - Test: Current Methodologies
  - Patients: All eligible patients
  - Targets: Full set of standard of care markers

Wave 2
- **Stream A**
  - Test: NGS panel (up to 50 genes / targets)
  - Targets: Community determined Essential & (Extended) targets
  - Patients: Potential for results to immediately inform management

- **Stream B**
  - Test: WGS
  - Targets: Many - Exemplar cancers
  - Patients: Potential for results to immediately inform management

Wave 3
- **Stream A**
  - Test: NGS panel (up to 150 genes / targets)
  - Targets: Community determined Essential & (Extended) targets
  - Patients: Potential for results to inform management at any point in pathway

- **Stream B**
  - Test: WGS
  - Targets: Many - Sufficient to justify an WGS approach on economic grounds
  - Patients: Potential for results to inform management at any point in pathway

Movement between streams possible after expert review

Assignment to a specific wave determined after expert review
This is just the beginning......

Expected increasing panel size with time until tipping point when WGS is more economic and fully validated

Pan-solid tumour panel(s) – CRC / NSCLC / CNS / melanoma / thyroid / phaeo / H&N / GIST / neurological

Pan-haematological tumour panel(s) – AML / MDS / MPN / ALL / myeloma / CLL / NHL

Karyotyping / FISH for haematological tumours & solid tumours

Reducing number of stand-alone tests retained eventually just for high sensitivity (MRD) & clinical emergencies

WGS – early adopters – Paediatric tumours, Sarcoma (some subtypes, Acute leukaemias

WGS – CRC

WGS other tumour types ?breast, ?lung, ?prostate

WGS – High grade serous ovarian, Cancer of unknown primary, Other haematological tumours where karyotype routinely performed

For indicative purposes only

The strategy has been designed as such that panel or WGS can be extended to new tumour types not currently included in the directory as new clinical data re utility emerges
Consolidating care to support genomics for all

- The Genomic Medicine Service connects and consolidates infrastructure in the NHS, including the service elements first developed to support the 100,000 Genomes Project.
- It will bring together existing clinical genetics services with NHS GMCs and the new Genomic Laboratory Hubs to provide seamless delivery of service across the nation.
Putting patients at the centre

• Progress in genomics has relied upon the active involvement and consent of participants, coupled with the support and understanding of broader society.

• Patients value and understand the power and potential of genomics, and significant engagement work has gone on in recent years to build understanding of its use.

• In such a fast-moving world, the support for genomics is not unquestioning and we recognise the ongoing need to invest time and effort to grow and nurture this support as the technology and its use advances.
Consent, choice and ethics

- As with all care, informed choice is the fundamental principle guiding use of genomics for patient benefit.

- The approach for genomic medicine is, effectively, just the extension of the existing approach to diagnostics but delivered through new technologies:
  - Patients (or guardians) consent to undertake testing for a particular clinical indication.
  - Depending on the testing method, there may be the possibility of additional findings. Patients can choose whether to receive these.
  - Patients are encouraged to allow their test to contribute to the knowledge base for research and treatment development. This research choice is separate – a slimmed down version of the approach used in the 100,000 Genomes Project.
  - Patients are given the choice to allow them to be re-contacted, should advances in knowledge provide fresh information about their condition.
Research participation to be routinely offered to all patients offered NHS diagnostic genetic test

- Creates **equitable access** to research offer (with consent)
- Includes recontact for invitations to further research, e.g. **clinical trials**
- Obtains **quality data & samples** for research
- Enables **scientific and medical discovery**
- Supports **learning, research & development** between NHS, academia, UK life science sector and internationally
- Informs **NHS process, pathway & data flow standardisation**
- Improves **quality, value and sustainability** of care
- **Involves patients and participants** throughout system, e.g. reviewing applications for research data use
As the diagnostic potential of genomics becomes clearer and personalised treatment options a reality, fresh consideration needs to be made of the health economics:

- New elements of value come into play
- A more dynamic approach to value needs to be made – with shares for diagnostics/drugs/payers/patients
- Standards of evidence must change – broader picture of clinical utility

**EXTRA VALUE THROUGH PERSONALISATION**

- Reducing adverse effects
- Reducing time delay in selecting optimal Tx
- Enabling Tx effective in a small fraction to be made available
- Increasing adherence/willingness to start Tx

*Adapted from: Can and Should Value-based Pricing be applied to Molecular Diagnostics, Office of Health Economics Apr 2012*
The genomic medicine journey to 2025

**Today:**
- Variable patient access to cutting-edge genetic technologies
- Proof of concept project demonstrating benefits
- ‘One size fits all’ treatment based on symptoms
- Limited use of genomic markers
- Diagnostic & clinical data not linked

**By 2020:**
- National Genomic Medicine Service driving personalised treatments and interventions with consistent & equitable access across the country – underpinned by a National Genomic Test Directory
- Improved diagnosis of rare conditions and better understanding of cancer
- Integrated informatics platform to support comprehensive linking of genomic and clinical data to give a full picture to patients
- Routine care and treatment closely linked through to clinical research, academia and industry with many more patients eligible for clinical trials

**By 2025:**
- New taxonomy of medicine based on underlying case & personal response
- Integrated clinical services taking a ‘whole pathway’ approach
- Routine use of Whole Genome Sequencing and newer genomic technologies embedded across multiple clinical pathways
- Genomics included as a fundamental part of clinical training across all professions and levels
- Tailored, optimised & more effective therapies for better outcomes