The Pathologist and the 100K Genomes Project

Mercedes Jimenez-Liñan
East of England NHS Genomic Medicine Centre
The 100,000 Genomes Project

Â Dec 2012: PM announced a project to sequence 100,000 Genomes from NHS patients with rare diseases and their relatives and patients with cancer.

Â Dec 2014: NHS England established first NHS Genomic Medicine Centres to coordinate activity across populations of ~5 million, working to common protocols & specification to ensure comparability and quality of data

Â 2015: Experimental cancer pathway developed early protocols

Â 2015: Cancer initiation phase starts, with experimental work to determine effectiveness of protocols

Â Feb 2016: Cancer Main Programme went live in 13 centres

Source: Genomics England
Each GMC is based within a lead NHS organization responsible for a specific geography.

The GMC works with other hospitals within their boundary as local Delivery Partners to ensure that as many eligible patients are recruited for the project.
Project Aims & Objectives

- 100,000 whole genome sequences with linked clinical data
- To obtain better diagnosis
- To tailor treatments to individual patients
- Transformation of the NHS with the implementation of genomic medicine into routine clinical care
- Increasing public knowledge and support for genomic medicine
What the NHS needs to contribute to the 100,000 Genomes Project

- Identification of eligible patients
- Inform and involve patients/public in ethics and consent
- Supply of processed DNA samples (blood and tumour) & multiomics
- Collection and collation of phenotypic clinical and diagnostic data
- Validation of WGS findings and feedback to patients

Source: Genomics England
Cancer sample requirements

- Germline DNA sample
- Tumour DNA sample
- Plasma for future non-fasting metabolomic studies and other biomarkers
- RNA-stabilised blood for future transcriptomic studies
- Serum for future proteomic studies and other biomarkers
- Plasma for future analysis of circulating-cell-free tumour DNA
# Approved List of cancers

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ovarian cancer</strong></td>
<td>All malignant epithelial tumours, sex-cord tumours, Germ cell tumours</td>
</tr>
<tr>
<td><strong>Lung cancer</strong></td>
<td>Small cell, Non small cell mesothelioma</td>
</tr>
<tr>
<td><strong>Prostate</strong></td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td><strong>Colorectal</strong></td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td><strong>Testicular cancer</strong></td>
<td>Germ cells and sex-cord tumours</td>
</tr>
<tr>
<td><strong>Breast cancer</strong></td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td><strong>Sarcoma</strong></td>
<td>Adult and paediatric sarcomas</td>
</tr>
<tr>
<td><strong>Renal cancer</strong></td>
<td>All carcinoma subtypes</td>
</tr>
<tr>
<td><strong>Adult brain tumour</strong></td>
<td>Gliomas of all cell types</td>
</tr>
<tr>
<td><strong>Hepatobiliary cancer</strong></td>
<td>All cell types</td>
</tr>
<tr>
<td><strong>Bladder cancer</strong></td>
<td>Urothelial cancer including Papillary urothelial cell carcinoma In situ</td>
</tr>
<tr>
<td><strong>Endometrial cancer</strong></td>
<td>All epithelial tumours and Endometrial stromal sarcomas</td>
</tr>
<tr>
<td><strong>Melanoma</strong></td>
<td>Primary and metastatic</td>
</tr>
<tr>
<td><strong>Upper GI tumours</strong></td>
<td>Gastric and small bowel cancers</td>
</tr>
</tbody>
</table>
Exclusion criteria for cancer

• Patients who have had chemotherapy, radiotherapy or endocrine therapy administered as normal clinical practice to treat that tumour type prior to biopsy or surgical resection

• Non availability of matched tumour and germline DNA samples.

• DNA of insufficient quantity or quality obtainable for Whole Genome Sequencing
Cancer Tumour Requirements

- Fresh frozen (FF) tissue should be collected wherever biologically possible

- FFPE samples may be submitted only if FF material cannot be collected

- Matched germline DNA sample from the patient’s peripheral blood
Ovary. FF – borderline component

Ovary. FFPE – invasive component
Multidisciplinary Team working

- Surgeons
- Nursing staff
- Biomedical scientists
- Pathologists
- Oncologists
- Staff in bioinformatics
Tumour Sample Handling

- Surgical specimens should be delivered unfixed to Pathology
- Samples cut-up within 2hrs of excision
- Samples can be maintained unfixed for 24 hours if rapidly cooled and kept at 4 degrees.
Morphology maintained

Tumour FF Time =0

Tumour FF VP 72hrs

Normal FFPE Time =0

Normal FFPE VP 72 hrs

slide courtesy of Dr. Louise Jones
Selection of Fresh Frozen (FF) samples

- The sample can be selected using a punch biopsy (5mm) or scalpel.

- If possible more than one punch/slice should be taken.
Ovary
FFPE Sample Handling

- Tumour too small for FF sample
  - Select genomic block from fresh specimen
  - Fixed for 12-24 hours

- Tumour too diffuse to select block from fresh specimen
  - Select block at cut up
  - Fixed for <36 hours

Controlled fixation is essential to minimise damage to nucleic acid
Blocks for DNA extraction should contain >40% viable neoplastic cells.

Areas with minimal necrosis and inflammation should be selected.

Macrodissection may be needed to obtain a suitable sample.
Omentum

Ovary
Omentum

High grade serous adenocarcinoma
Tumour histopathology assessment module

- All individuals assessing tumour percentage and cellularity should participate in the UK NEQAS pilot on-line tumour assessment programme.

- To standardised identification of cancer:
  - Assess the adequacy of a sample for testing
  - Estimation of cellularity
  - Estimation of tumour content
  - Macrodissection mark up
Tumour histopathology assessment module

- Tumour types included
  - Breast, colorectal, lung, ovarian, prostate

- Two assessments per year

- Option to participate in selected tumour types
Genomic analysis of diagnostic biopsies ('genomic biopsy')

- Analysis of chemonaive tissue in patients treated with neoadjuvant chemotherapy

- Inclusion of patients not undergoing surgical resection.

- Analysis of some of the most aggressive tumour types
Diagnostic biopsies - Consent

- Fully informed consent in line with the 100,000 Genomes Project Protocol

- Generic consent for taking an additional research biopsy or use of surplus diagnostic biopsy material for research
Genomic biopsy – sample handling

- Diagnostic biopsy → placed in formalin
- Genomic biopsy → stored at -80°C
- Genomic biopsy should not be processed until cancer diagnosis is made on histology
- Frozen section should be taken to assess tumour cellularity
Genomic biopsy – sample requirements

- Limited DNA yield
- If possible more than one biopsy should be taken.
- Variable tumour content
- Macrodissection for tumour enrichment
- FF material is recommended
Breast biopsy

Invasive carcinoma NST
Breast wide local excision
100,000 Genomes Project

WGS data from ILLUMINA

WGS data to GEL + GECIP Interpretation partners (Congenica, Omicia, WuXi): Interpretation of Data

RESULTS TO GMC LAB DISCUSSED AT ONCOGENETICS BOARD
Discussion regarding actionable mutations present

- Validate actionable mutations in accredited lab

Somatic: Molecular Malignancy Lab

Germline: Clinical Genetics

Validated results presented to ONCOGENETICS BOARD
Agreement on results to action

Results into EPIC (Medical records)

Final results reported to MDT
Agreement on Action Plan

PATIENT
Feedback +/- treatment change

Result summary to GEL

Flow Chart Design Jean Abraham
Composition of Oncogenetics Board

- Pathologist
- Clinical Genetics Counsellor and Consultant
- Medical / Clinical Oncologists
- Molecular Diagnostics Laboratory team members
- Co-ordination/administration team
Genomic Education Programme – NHS Health Education England

On line education courses
- Sample processing and DNA extraction
- Fundamentals of genomics
- Bioinformatics
- How to support patients through consent process

Master in Genomic Medicine
- The programme is aimed at NHS healthcare professionals (medicine, nursing, healthcare scientists and technologists).

www.genomicseducation.hee.nhs.uk