Realising the potential of genomics

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Genomics England
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“It is crucial that we continue to push the boundaries and this new plan will mean we are the first country in the world to use DNA codes in the mainstream of the health service.”

The Rt Hon David Cameron MP
The Prime Minister
10 December 2012
Four main aims

1. To bring benefit to NHS patients
2. To create an ethical and transparent programme based on consent
3. To enable new scientific discovery and medical insights
4. To kickstart the development of a UK genomics industry
Principal Partners

NHS England and GMCs

GeCIP

Genomics England

Illumina

Industry Partnerships

Delivering the programme in:
- Rare disease
- Cancer

Genomics in infectious disease
The Rare Disease Programme
The scale of rare diseases

1 in 17 people will suffer from a rare disease at some point in their lives.

In the UK alone that equates to approximately 3.5 million people.

Only a quarter of rare diseases have had their molecular basis defined, meaning many risk being undiagnosed and therefore untreated.

There are at least 6,000 rare diseases.

Many rare diseases (approximately 80%) are of genetic origin.

Seventy-five per cent of rare diseases affect children.

30% of rare disease patients die before their fifth birthday.
Why make genetic diagnoses?

1. **For the patient**
   - Understand why their condition happened
   - More accurate knowledge of how it might develop in future
   - Possible treatment avenues
   - Contact with others with the same condition

2. **For the family**
   - Predict whether family members will get the condition
   - Offer screening/treatment to prevent it
   - Reproductive decisions

3. **For medical research**
Impact of making diagnosis

High cholesterol, but young and slim so still quite ‘low risk’

Management?

Dietary advice
Consider small dose of statin if no response to diet

Outcome?

Patient dies of myocardial infarction aged 42
Taking a family history

- Died of MI, Age 56
- Died of MI, Age 45

Diagnosis: familial hypercholesterolaemia
Confirm by doing a genetic test
Treatment: lipid clinic referral, high dose statin
Cascade testing

- Died of MI, Age 56
  - Died of MI, Age 45
  - 40 TC 7.6, BMI 23
  - High chol
  - On statin
Research insights from rare disease genetics: **PCSK9**


Loss-of-function mutations cause low cholesterol (2006)

An individual with no functioning copies of **PCSK9** was found who is healthy and has very low cholesterol

Knocking out PCSK9 could lower cholesterol

Knocking out PCSK9 is unlikely to cause serious side-effects

Treatment trials of anti-PCSK9 drugs are now underway: they lower cholesterol and have a good side effect profile. These drugs work for everyone with cholesterol, not just in familial hypercholesterolaemia.
Rare disease programme

Disorders nominated by the NHS and academia

171 disorders so far

Eligibility criteria: describe which patients to recruit

Data model: describes the clinical information to be collected for each disorder

Gene panel: the genes to be analysed first for patients with that disorder
PanelApp
https://bioinfo.extge.co.uk/crowdsourcing/PanelApp/

**Public access**
- View and download gene panels.
- View Reviewers’ comments.

**Register to be a reviewer**
- View and download gene panels.
- View Reviewers’ comments.
  - Evaluate genes and make comments.
  - Add genes to a gene panel.
## 17 genes

17 of 17 reviewed

<table>
<thead>
<tr>
<th>List</th>
<th>Gene</th>
<th>Reviews</th>
<th>Mode of inheritance</th>
<th>Source of Evidence</th>
<th>Phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>BTK</strong></td>
<td>4 reviews</td>
<td>X-LINKED: hemizygous mutation in males, monoallelic mutations in females may cause disease (may be less severe, later onset than males)</td>
<td>Illumina TruGenome Clinical Sequencing Services, UKGTN, Radboud University Medical Center, Nijmegen</td>
<td>Agammaglobulinemia, X-linked: Agammaglobulinemia, X-linked 1, 300755Agammaglobulinemia and isolated hormone deficiency, 307200</td>
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<tr>
<td>Green</td>
<td><strong>PIK3R1</strong></td>
<td>4 reviews</td>
<td>Not set</td>
<td>Radboud University Medical Center, Nijmegen, UKGTN</td>
<td>Agammaglobulinemia 7, autosomal recessive, 615214SHORTH syndrome, 269880</td>
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<tr>
<td>Amber</td>
<td><strong>BLNK</strong></td>
<td>3 reviews</td>
<td>Not set</td>
<td>Radboud University Medical Center, Nijmegen</td>
<td>Agammaglobulinemia 4, 613502</td>
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</tbody>
</table>
Who do we sequence?

Different genetic diseases have different inheritance patterns.

Comparing which genetic variants are found in each family member helps to identify disease-causing mutations.
Data interpretation: the biggest challenge in genomic medicine

- ~5-10 million variants in our genome
- ~3.5 million “known” SNPs
- ~0.5 million “novel” SNPs
- ~0.5 million small indels
- ~1000 large (>500bp) CNVs
- ~20,000-25,000 coding variants
- ~9,000-11,000 non-synonymous
  - 92 rare missense variants (MAF <0.1%)
  - 5 rare truncating variants (MAF <0.1%)
  - 0-2 de novo variants
What information do you need to find the disease-causing variant?

The prior probability is in favour of a variant NOT causing disease

- How common is the variant in the ‘healthy’ population?
- Has the variant been seen before in people with the same disease?
- Does the variant cause a big change in the protein sequence produced by the gene?
- Is the variant present in the family members with the disorder, and not in those without it (segregation)?
- Has the gene been associated with this disorder before?
- Is there any information about what the gene does?
‘Omic’ samples
Transcriptomics, metabolomics, proteomics

Samples being collected for RNA, serum and plasma

Designed to assist with:
  • Variant interpretation eg splice site mutation effects
  • Research into biomarker development

Also cell-free DNA in the cancer programme

Sample processing is complex
  • Need for rapid spinning and freezing
  • Difficult to assess quality and shelf-life of samples
  • Need fresh blood samples from all participants

Pushing the boundaries to maximise the chance of translating project results for clinical benefit
The Cancer Programme
Cancer is a genetic disease
Most cancer is NOT inherited

In inherited cancers, this first mutation may be present in all of the body’s cells

Other mutations happen spontaneously, or because of environmental factors eg radiation
Sequencing cancer genomes

Tumour genome sequence

Constitutional genome sequence

Driver mutations
Random mutations because cancer genomes are unstable
Mutations caused by chemotherapy or radiotherapy

Tumour variants = Constitutional variants = Somatic variation
Cancers contain different clones of cells

Each clone of cells has a different genome

The sequence results will be different depending where you take your biopsy or sample from

BRAF inhibitors in melanoma

BRAF V600E is a driver mutation in around 50% of melanomas (2002)

Drugs have been developed for use in tumours which have this mutation

Nikhil Wagle et al. JCO 2011;29:3085-3096
Cancers included in the programme

Common cancers included initially:

- Lung
- Breast
- Ovarian
- Prostate
- Colorectal

Others being added: renal, sarcoma, childhood cancer

Familial predisposition to cancer is part of the rare disease programme
Molecular pathology

Complex NHS transformation underway

Tumour samples are traditionally preserved in formalin then fixed in paraffin (FFPE) to preserve cellular architecture for diagnosis under the microscope.

DNA extracted from samples treated like this is damaged and broken.

- Use part of the sample for FFPE and histology.
- Freeze part of the sample for genetic tests.
  - Need to make sure the sample contains mainly tumour cells.

This new pathway requires very significant changes in sample handling, affecting surgeons, interventional radiologists, pathologists and oncologists.
Cancer results

A small number of clinically actionable driver mutations with treatments known to work/not work [may already have been tested for in the clinical context]

Germline results which affect cancer development

eg a BRCA1 mutation in a patient with breast cancer but without a strong enough family history to be tested for BRCA1 in the genetics clinic

Remainder of results are mostly of research interest for now, but in future may assist:

- Drug development
- Targeted treatment selection
- Prediction of prognosis
- Monitoring of disease progression
Genomics in Infectious Disease
Uses of genomics in infectious disease

• Detailed classification of infectious agents (no culture needed)
• Identify factors contributing to transmission by studying individual transmission events
• Monitor pathogen evolution and adaptation such as antimicrobial resistance eg in TB
• Early identification of pathogens with epidemic potential
• Refine strategies for epidemic control
Phylogenetic analysis of the 2014 ebola outbreak

Vitali Sintchenko, and Edward C Holmes BMJ 2015;350:bmj.h1314
Implementation of the Project
NHS Genomic Medicine Centres

• 13 Genomic Medicine Centres covering England
• Partnerships of NHS Trusts within the region
• Responsible for identifying and recruiting participants
• Co-ordinate clinical care following results
NHS Genomic Medicine Centres
- Clinical samples and hospital data
- Laboratory processing including molecular pathology
- Broad consent for research and re-contact

Participants
- NHS England

Oversight:
- Department of Health

Funding:
- National Institute for Health Research
- Wellcome Trust
- MRC Medical Research Council
- Cancer Research UK

Data
- Clinical Data
  - Identifiable clinical data
  - Longitudinal
  - Linked to genomic data
- Research Data
  - Pseudonymised
  - GeCIP and industry partners work within data centre

Existing Clinical Data
- Cancer &RD registries, HES, Mortality data, etc

Data and Analysis Improvement
- Annotation & QC
- Scientists/SMEs
- Product comparison

Clinicians & Academics
- Training
- Industry

Fire wall
Establishment Phase

- Illumina - NHS Genomic Medicine Sequencing Centre in Hinxton
- UK Data Infrastructure for Genomic Medicine (with MRC)
- NIHR National Biosample Centre - £24 million state-of-the-art facility to store the samples
Consent conversation

Takes around 45-60 minutes to recruit each family

Description of the project
Information about uses of clinical and genomic data
  • Lifelong health records linkage
  • Access to de-identified data for academia and industry
  • Insurance implications
Recontact for future samples, information and research
Results – implications for family members
Withdrawal from the project
What will we be telling participants?

- Information about a patient’s main condition

- Information about ‘serious and actionable’ conditions (optional)

- Carrier status for adults who might have future children (optional)

Image courtesy of Health Education England
Additional findings offered in the 100,000 Genomes Project

**Bowel cancer predisposition:**
- MLH1 (adult only)
- MSH2 (adult only)
- MSH6 (adult only)
- APC (adult and child)
- MUTYH (adult only)

**Breast and ovarian cancer predisposition:**
- BRCA1 (adult only)
- BRCA2 (adult only)

**Other cancer predisposition:**
- VHL (adult and child)
- MEN1 (adult and child)
- RET (adult and child)

**Familial hypercholesterolaemia:**
- LDLR (adult and child)
- APOB (adult and child)
- PCSK9 (adult and child)

**Autosomal recessive carrier status:**
- CFTR (Cystic fibrosis)

**OPTIONAL!**

**Requirements:**
- Reliably detected by genome sequencing
- Curated list of high confidence, high penetrance variants
- Treatable or preventable condition

Other conditions may be added if clinically appropriate and technically feasible
Genomics England Clinical Interpretation Partnership (GeCIP)

Working with the research community

• Launched at the Wellcome Trust in June 2014
• Partnership between over 2,500 researchers from academia and the NHS, trainees, plus international collaborators
• Designed to accelerate academic/industry partnership and development of diagnostics and therapies
• Over 30 topics (domains) of research; most domains cover a single disease or group of diseases and some are wider; these include epigenomics, health economics and technology
• All data generated contributes to the Genomics England Dataset
Patient and public participation

PPI groups contribute to the project within each GMC

Participant panel being recruited by Genomics England

- Members will sit on committees including the data Access Review Committee
- Some members have professional experience in a relevant field in addition to being participants in the programme
GENE Consortium

Working with industry

• 11 companies have come together to create the Genomics Expert Network for Enterprises (GENE) Consortium to oversee a year-long Industry Trial

• Aims to identify most effective and secure way of bringing industry expertise into the 100,000 Genomes Project in order to realise the potential benefits for patients

• AbbVie, Alexion, AstraZeneca, Berg, Biogen, Dimension Therapeutics, GSK, Helomics, Roche, Takeda, NGM Biopharmaceuticals
Health Education England

Upskilling the workforce

• 9 University providers of MSc in Genomic Medicine – aimed at NHS healthcare professionals working in England
• Genomics Education Programme
• Online training courses and resources
Leslie Hedley, 57

WGS revealed Mr Hedley’s kidney failure was caused by a particular genetic variant (INF2 mutation). His family is also being tested and their blood pressure can now be effectively controlled by drugs available on the NHS.
First children receive diagnoses (GOSH)

Georgia Walburn-Green, aged 4

Jessica Wright, aged 4

DNA breakthrough gives sick children new hope

First children diagnosed in 100,000 Genomes Project

First genome project diagnoses give hope to two four-year-olds

Children suffering mystery illnesses finally diagnosed through gene screening