Genetics and Diagnostics in the NHS

Welcome to Century 21

Shehla Mohammed
Genomic Medicine

- How can it be achieved?
- Current good models?
- Strategy
- Challenges
- Solutions
Genetics and integration with other specialties: background

- Reports by PHG Foundation
- **Genetics and mainstream medicine: service development and integration**
  [http://www.phgfoundation.org/reports/7965](http://www.phgfoundation.org/reports/7965)
- Whole genome sequencing; clinical impact and implications for health services
- **Next steps in the sequence**
  [http://www.phgfoundation.org/reports/10364](http://www.phgfoundation.org/reports/10364)
Genomics in Medicine

Delivering genomics through clinical practice

Report of the Joint Committee on Medical Genetics

June 2012
Current excellent models

- Cardiology
- Ophthalmology
- Metabolic
- Genetics
- Dermatology
- Cancer
- Neurology
- Endocrine
Why do we do genetic tests?
Genetic testing in the clinic

- Focus has been to identify gene mutations that cause rare disease
- Now we are able to look at rare and common diseases and identify gene mutations that will influence management of the patient
Whole Genome Approaches

- Chromosome size (100 Mb)
- Conventional G-banding karyotype resolution (10 Mb)
- Molecular karyotype resolution (100 kb)
- Deep sequencing resolution (1 bp = 1 mm)

From: Stephenson et al J R Soc Interface. Sep 8. 2010
Genetics Has Changed

Moore's Law

$ per Mb DNA Sequence

Sequencing

**Whole Genome Sequencing**
3 billion base pairs
- Last year £16,000
- This year £4,000

**Whole Exome Sequencing – all protein coding regions**
30 million base pairs
- Last year £1,500
- This year £600

**Gene panel Sequencing – a selection of clinically relevant genes**
100,000 base pairs
- Last year £500
- This year £150

(without on-costs)
Applications in Diagnostics

Current Paradigm

Clinical Assessment → Individual Gene Test

Repeat through all known disease causing genes until pathogenic mutation found

Future Paradigm

Clinical Assessment → All Genes Sequenced → Individual Genes Tested in silico

Repeat through all known disease causing genes until pathogenic mutation found
Current Prices of Genetic Tests in the UK

<table>
<thead>
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<th>Gene Panel</th>
<th>Exome</th>
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Number of tests

Price
## Success of Exome Sequencing in Research

<table>
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<tr>
<th>Disorder</th>
<th>Gene(s)</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Four Limb Lymphoedema</td>
<td>GJC2</td>
<td>Ostergaard et al <em>J Med Genet</em> 2011</td>
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<td>Hajdu Cheney Syndrome</td>
<td>NOTCH2</td>
<td>Simpson et al <em>Nat Genet</em> 2011</td>
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<tr>
<td>Familial AML</td>
<td>GATA2</td>
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<td>Generalised Pustular Psoriasis</td>
<td>IL1F5</td>
<td>Onoufriadis et al <em>Am J Hum Genet</em> 2011</td>
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<tr>
<td>Microcephaly, Lymphedema, Chorioretinal Dysplasia</td>
<td>KIF11</td>
<td>Ostergaard et al <em>Am J Hum Genet</em> in press</td>
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</table>
Outcomes: case study (rare disease)

- 3 yr old boy with short stature, slow weight gain and enlarged liver
- Repeated tests, genetic studies, liver biopsy: GSD ? type
- 16 yrs: no definite diagnosis
- Family seeking advice: risk for normal siblings off-spring?

**NGS panel testing: GSD VI**

| Lab tests over 12 yrs | £ 2800 |
| Consultations        | £ 6120 |
| Liver biopsy, EMG    | £ 2877 |
| Genetic test for GSD 1X | £ 3000 |
| **Total costs over 12 yrs without GSD panel test** | **£ 14797** (No definitive diagnosis) |
| **Total cost with GSD 18 gene panel genetic tests** | **£4860** saving of **£9,937** (Definitive diagnosis made) |
"One in a billion: A boy's life, a medical mystery"

2011 Pulitzer prize for explanatory reporting
Lessons from rare disease genetics

- Genetic discoveries
  - Greater understanding of biological mechanisms targeted treatment for rare diseases
  - Research into treatments for genetic subtypes of common diseases may lead to benefits.

- Clinical implementation
  - The validity and utility of the genetic test needs to be considered before use in clinical pathway
Outcomes: case study (common disease)

- Breast cancer
- 1 in 9 of the female UK population
- Treatments now being influenced by gene testing (BRCA1, BRCA2)
- Sequencing of individual cancer genomes to customise treatment
  - Driver and passenger mutations
  - Oncogene targeted therapy
Cancer classification - conventional

Cancers are classified based on:

- anatomical site of origin
- morphology
- tumour size
- tumour grade
- spread (lymph nodes etc)
- hormone receptor status
Breast cancer – Conventional classification (Goldhirsch et al, 2011)

A - Low proliferation
Endocrine therapy only

Luminal
ER,PR+

B - High proliferation
Chemotherapy + endocrine therapy

Her-2 amplified
Chemotherapy + Trastuzumab

ER,PR,Her2-ve
Chemotherapy

15-20% of all breast cancers are "triple negative"
Cancer classification - genomic

Estimated that tumors have 5 - 7 driver mutations with a dominant driver and subclones

Driver: contribute to cancer development, confer growth advantage, have been selected, may confer drug resistance

Mutations are randomly distributed across genome

Mutation rate influenced by: CGATT

- About 2000 cancer genomes fully sequenced worldwide
- Number of mutations varies from 1000 – 10,000 in most adult cancers or to ≥100 000 (lung cancer, melanoma)
- Most mutations are passenger mutations

Resistant disease and metastases are subclones of primary cancer

*From: Cancer as a disease (M Stratton, Science 2011)*
Breast cancer rules rewritten in 'landmark' study

- The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups
  
  *Curtis et al Nature 18 April 2012*

- Novel molecular stratification
- Breast cancer is 10 different diseases
- Tailored management
- Better survival prediction
## The future: Use of cancer genome to personalize treatment

<table>
<thead>
<tr>
<th>At diagnosis</th>
<th>After treatment</th>
<th>At relapse</th>
<th>If metastases develop</th>
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<tr>
<td>CATTGCGA</td>
<td>CGTATCCGC</td>
<td>ATGCTAACAT</td>
<td>ATGCTAACAT</td>
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</table>

Sequence whole cancer genome to determine set of relevant driver mutations and targetted therapy.

Determine predictors for toxicity.

Monitor minimal residual disease using passenger mutations.

Resequence relapse to determine relevant driver mutations for therapy.

Resequence metastases to determine relevant driver mutations for therapy.

Subclone new mutation.
Summary

- Cancer classification will be determined by cancer genome
- Cancer treatment will be tailored to the cancer genome and genetic make-up of patient
- Patients will be spared ineffective treatment
- However, a large pool of targeted drugs and diagnostic tests will be required to personalize cancer diagnosis and treatment
# New Genetic test recommendations for NHS service from April 2012

<table>
<thead>
<tr>
<th>Description</th>
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<td>Gene Dossiers evaluated 2011</td>
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<td>Gene Dossiers recommended and approved</td>
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<td>Gene Dossiers with savings across diagnostic care pathways</td>
<td>29</td>
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<tr>
<td>Gene Dossier with less than 50 referrals per annum</td>
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</table>
Gene Dossiers 2012/13
Total submissions = 77

Themes
Panel tests incorporating multiple genes & conditions
NGS : 8-105 genes per panel

- Endocrinopathies = 8 genes
- DNA repair disorders = 12
- CMD = 22
- Retinopathies genes = 105 genes

- Quality Assurance : best practice guidelines

- NIPD : single gene disorders
- GD’s for recently identified genes
Human Genomics Strategy group (HGSG)

Policy for expansion of genomic technology
White Paper and commissioning of:

• **Genomic Technology Centre** (centers of excellence, translating research protocols into service, knowledge dissemination to Biomedical Hubs and Regional genetics centers)

• **Biomedical Diagnostic Hub** (integrated molecular diagnostic testing for pathology and genetics)

• **Regional Genetics Centre** (patient link - diagnosis of inherited disorders, counselling, expert genetic advice)

Challenges

- Enabling access
- Working across specialty boundaries
- Financial constraints
- Education
Solutions

- Developing a diagnostic pipeline (whole exome and gene panels)
- Access by users of service
- Developing operational models for clinical pathways
- Quality assured, interpretive results
- Translational research opportunities