Many Genomes Impact Health

- Human Genome

- Pathogens, Vectors, Model Organisms,
Cancer Genome: acquired (somatic) variation

Constitutional Genome:

Human Genome Variation and Health
Medical Applications of Genetics & Genomics

- Aetiology
  - Genetic insights into biology of disease
    - Diagnosing Mendelian & chromosomal disorders
    - Stratified medicine

- Diagnostics
  - Pharmacogenetics
  - Targeted therapy & prevention

- Therapeutics

Medical Applications of Genetics & Genomics

- Genetic insights into biology of disease
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- Therapeutics
Advances in testing the Genome: Resolution, Speed and Cost

- Karyotype
  - ≈ 5x10^6 bp resolution
  - Culture cells

- NEXT GENERATION SEQUENCING
  - 1bp resolution
  - Hours/Days

- array CGH
  - ≈ 10^3 bp resolution
  - No cell culture
'Next generation' sequencing technology introduced
Inherited Disorder

Single Gene

Multiple phenotypic effects

Common Disorder With Genetic Contribution

Many Different Genes Involved

Shared Phenotype
Inherited Disorder

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Multiple phenotypic effects

Common Disorder
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Stratified Medicine

Shared Phenotype
Inherited Disorder

- Single Gene
- Multiple phenotypic effects

Common Disorder With Genetic Contribution

- Many Different Genes Involved
- Shared Phenotype

- Precision Diagnosis
- Targeted Treatment
Diagnostic Applications of Next Generation Sequencing

**Gene Panels**
- Few to 100s of Genes, e.g.
  - Cancer genes
  - Epilepsy genes
  - Eye disorders

**Exomes**
- All ~25,000 Genes
  - <2% of genome
  - "Clinical Exome" = 4800 known disease genes

**Genomes**
- All 3 Billion bp of DNA
  - Identifies genetic variation including in the 98% of ‘Junk’ DNA

Phenotype driven diagnostics
Most NHS Diagnostic centres

DDD Project
Some Diagnostic Centres

"100,000 Genomes"
Genomic Diagnosis of Inherited Disease
Genomic Diagnosis of Inherited Disease

Retinitis Pigmentosa

? X-LINKED, ? Autosomal Recessive
176 Gene Panel for Retinal Degeneration

- Homozygous pathogenic mutations in *IMPG2* - **Autosomal Recessive RP**
- Very low risk to daughter’s future children
Deciphering Developmental Disorders: A UK-Wide Project: Exome Sequencing and aCGH

- 12,000 previously investigated children with undiagnosed developmental disorders
- Parental samples for comparison
- Specific genetic diagnosis made in 35%
- Now the NHS has to catch up!
Exome Sequencing in the NHS:

• Building on research experience
• Health and Care Research Wales implementation and evaluation project
• NHS Genetics Laboratory UHW
• Wales Gene Park
• Technical and Bioinformatic skills and resources
Array Comparative Genomic Hybridisation (aCGH)

- 2 yr old child
- Seizures
- Severe developmental delay

Lots of tests already done, but no diagnosis

aCGH detects a genetic cause in ~20% of patients with developmental disorders
A Very Small Deletion at Chromosome 14q12
A 2.3kb deletion of **FOXG1**

Approx. 60 patients with FOXG1 deletions from the medical literature
Genomics and Common Disease
e.g. Prevention, Diagnosis and Treatment of Cancer

• Identification of people at high risk for offer of increased screening / prophylactic treatment (e.g. BRCA genes, Lynch syndrome etc.) – constitutional

• Tumour testing mutations conferring sensitivity or resistance to drug treatment – somatic (acquired)
KRAS/NRAS Gene Testing in Advanced Bowel Cancer

• Tests for somatic (acquired) mutations in the tumour

• Cetuximab blocks EGFR and improves survival in SOME patients (about £40K per year)

• Doesn’t work if the cell signalling pathway is activated by KRAS/NRAS mutation – present in 40%

• Medical Genetics tests > 1000 bowel cancer samples / yr
Genetic Stratification of Other Cancers

- Metastatic melanoma
  - BRAF mutation and Vemurafenib
- Non small cell lung cancer (NSCLC)
  - EGFR mutation and Erlotinib
Testing Cell Free DNA: Applications in Prenatal Diagnosis and Cancer

- Non invasive prenatal diagnosis of rare inherited and chromosomal disorders
- For stratified medicine treatment and monitoring of cancers
Targeted Treatment of Rare Inherited Disorders

Two examples from Institute of Medical Genetics

Diagram:
- Disease
- Gene(s)
- Functions Pathways
- Drug Interventions

The diagram illustrates the relationship between disease, gene(s), functions pathways, and drug interventions.
X-Linked Hypohidrotic Ectodermal Dysplasia (XL-HED)
## EDI200 Treatment in XL-HED

<table>
<thead>
<tr>
<th>A Physiological Process</th>
<th>The Medical Problem</th>
<th>EDI200: Edimer’s Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Processed soluble EDA-A1</td>
<td>EDA-A1 Deficiency</td>
<td>EDI200</td>
</tr>
<tr>
<td>Sweat glands, teeth, and hair</td>
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<td>EDA-A1</td>
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**Fusion of Ectodyplasin (EDA-A1) to IgG heavy chains provides clumping needed for receptor activation and transplacental transfer for future prenatal trials**
EDI200 Correction of Teeth & Oesophageal Glands in Dogs with XLHED

Unaffected | XLHED-Unreared | XLHED-Treated

Permanent Teeth

Oesophageal Glands

Casal 2007
Mauldin 2009
EDI200 International Phase II Trial in XL-HED Newborn

- EDIMER pharma, lay societies, expert centres
- Recruitment during pregnancy (family history)
- Antenatal scan 26/40 – sex and jaw for tooth buds
- Genotyping on cord blood (result in 48 hrs)
- Family and baby travel to Cardiff
- Treatment starts before day 14
- 5 iv infusions over 2 weeks
- Outcomes: Safety, dentition, sweat glands
Tuberous Sclerosis: Tumours, Epilepsy, Autism, Learning Problems

Kidney

Brain

Epilepsy
Tuberous Sclerosis (TSC) Gene Mutation Causes mTORC1 Activation in Cells & Drives Disease Process
TSC Brain and Kidney Tumours Respond to Everolimus

**EXIST-1**

**BRAIN**

**EXIST-2**

**KIDNEY**

Best % change from baseline (sum of volumes of target lesions)

**Everolimus (n = 76)**

**Placebo (n = 39)**

Epilepsy in TSC Improves with Everolimus Treatment

23 subjects enrolled

20 subjects eligible to begin treatment

20 subjects completed main treatment phase

12 subjects
Seizure reduction > 50%

3 subjects
Seizure reduction 25–50%

5 subjects
Seizure reduction < 25%

1 treatment with alternative antiepileptic drug
2 with insufficient seizures

EXIST-3: RCT of everolimus in refractory epilepsy in TSC is underway

Neurocognition in TSC?

- RCT of Everolimus
- Patients aged 16 years plus
- Neurocognitive & medical assessments
- Diffusion Tensor Brain MRI
- Parallel trials in younger TSC patients in USA and Netherlands
“the human genome sequence offers a unique opportunity to understand genetic factors in health and disease, and to apply this rapidly to prevention, diagnosis and treatment”

Francis Collins, Director NHGRI
to US House of Representatives, May 2003