Genetics and the Future of Medicine

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Translational Research Institute,
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Outline

• Genetic technology has in the research sector massively progressed in the past decade
  – Microarrays
  – Massive parallel sequencing.
• This has enabled
  – Identification of common and rare disease genes and development of genetic screening methods
  – Comprehensive cancer sequencing enabling cancer personalised medicine.
• These developments are now ready to transfer into clinical practice, and will change medical practice subst
Human Genetic Diseases

• Single gene ‘monogenic’ diseases
  – e.g. cystic fibrosis, haemochromatosis, osteogenesis imperfecta
  – Generally rare
  – Each family usually has a different mutation, usually in the same gene
  – Evident inheritance from generation to generation.
Fibrodysplasia Ossificans Progressiva (FOP)

A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva

Eileen M Shore1–3, Meiqi Xu1,2, George J Feldman1,2, David A Fenstermacher1–6, Tae-Joon Cho7, In Ho Choi7, J Michael Connor6, Patricia Delaí10, David L Glaser1,2, Martine LeMerrer10, Rolf Morhart11, John G Rogers12, Roger Smith13, James T Triffitt14, J Andoni Urtizberea15, Michael Zasloff1,2,16,17, Matthew A Brown14,18 & Frederick S Kaplan1,2,19

NATURE GENETICS VOLUME 38 | NUMBER 5 | MAY 2006
ACVR1 and FOP

- Nearly all cases have a single point mutation in ACVR1 (R206H)

- The structure of ACVR1 has now been resolved.
  - This has led to the identification of a lead compound for development of ACVR1 inhibitors.
• The Human Genome Project took
  – ~12 years to complete a single genome
  – an army of scientists
  – ~US$3.8 billion.
Economics of Genomics

• $3.8 billion investment in Human Genome Project has led to:
  – $965 billion output from the genomics industry
    • 178:1 economic return
  – Created 4.3 million US job years employment
  – In 2012 alone genomics sector contributed $6.0 billion in US tax revenue
    • More than the entire 13 year investment in HGP.

Battelle Technology Partnership Practice, June 2013.
Anti-sclerostin antibodies

Cathepsin K antagonists
# Osteoporosis Drug Targets and Genetics

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug Target</th>
<th>Monogenic Condition</th>
<th>Common variant association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td>Farnesyl Pyrophosphate</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>SERMs</td>
<td>Estrogen Receptor</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Estrogen Receptor</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>DKK-1 Inhibitors</td>
<td>DKK-1</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Cathepsin-K inhibitors</td>
<td>Cathepsin-K</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Denosumab</td>
<td>RANKL</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Sclerostin inhibitors</td>
<td>Sclerostin</td>
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<td>Yes</td>
</tr>
<tr>
<td>PTH analogues</td>
<td>PTH receptor</td>
<td>Yes</td>
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</tbody>
</table>
Sequencing Becomes Affordable

• Costs of sequencing dropping more rapidly than 50% per annum

• Cost now <$1500 / genome

• Likely to cost less than an MRI scan by 2015.
Sequencing for Single-Gene Diseases

- Benefits the individual and family
  - Provides an accurate diagnosis
  - Gives a chance for rationally designed, targeted treatment
  - Enables antenatal diagnosis.

- Benefits the community
  - Is informative about human biology and can point to new treatments for common diseases.

- Currently only 1/8 genetic conditions known have a test available for them in Australia.
Mapping Monogenics By Sequencing

• Ng et al, Nature Genetics, 2010
  – Used hybridization capture to pull down exomes
  – Sequenced using Illumina Solexa sequencer.
  – Studied 4 cases (2 sibs plus 2 unrelated) with Miller Syndrome, a previously unmapped monogenic disease.
  – Filtered SNPs according to whether they were in dbSNP or in 8 controls sequenced.
### Mapping Monogenics By Sequencing

Exome sequencing identifies the cause of a mendelian disorder

Sarah B Ng¹,¹⁰, Kati J Buckingham²,¹⁰, Choli Lee¹, Abigail W Bigham², Holly K Tabor²,³, Karin M Dent⁴, Chad D Huff⁵, Paul T Shannon⁶, Ethylin Wang Jabs⁷,⁸, Deborah A Nickerson¹, Jay Shendure¹ & Michael J Bamshad¹,²,⁹

<table>
<thead>
<tr>
<th>Filter</th>
<th>Kindred 1-A</th>
<th>Kindred 1-B</th>
<th>Kindred 1 (A+B)</th>
<th>Kindreds 1+2</th>
<th>Kindreds 1+2+3</th>
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<tbody>
<tr>
<td></td>
<td>Dominant</td>
<td>Recessive</td>
<td>Dominant</td>
<td>Recessive</td>
<td>Dominant</td>
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<tr>
<td>NS/SS/I</td>
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<td>2,863</td>
<td>4,687</td>
<td>2,859</td>
<td>3,940</td>
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<tr>
<td>Not in dbSNP129</td>
<td>641</td>
<td>102</td>
<td>647</td>
<td>114</td>
<td>369</td>
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<td>Not in HapMap 8</td>
<td>898</td>
<td>123</td>
<td>923</td>
<td>128</td>
<td>506</td>
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<tr>
<td>Not in either</td>
<td>456</td>
<td>31</td>
<td>464</td>
<td>33</td>
<td>228</td>
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<tr>
<td>Predicted damaging</td>
<td>204</td>
<td>6</td>
<td>204</td>
<td>12</td>
<td>81</td>
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</tbody>
</table>

• One only candidate remained, DDOH
  – Dihydroorotate dehydrogenase.
Multicentric Carpotarsal Osteolysis is Caused by Mutations Clustering in the Amino-Terminal Transcriptional Activation Domain of MAFB

Andreas Zanli, Emma L. Duncan, Paul J. Leo, Graeme R. Clark, Evgeny A. Glazov, Marie-Claude Addor, Troels Herlin, Chong Ae Kim, Bruno P. Leheup, Jim McGill, Steven McTaggart, Stephen Mittas, Anna Mitchell, Geert R. Mortier, Stephen P. Robertson, Marie Schroeder, Paulien Verdel, and Matthew A. Brown

The American Journal of Human Genetics 90, 494–501, March 9, 2012

<table>
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<tr>
<th>SKDP 1.3</th>
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<th>SKDP 20.4</th>
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<th>SKDP 8.3</th>
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<td>Variants</td>
<td>58734</td>
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<td>59195</td>
<td>50507</td>
<td>55802</td>
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<td>After QC</td>
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<td>27818</td>
<td>28804</td>
<td>22545</td>
<td>24795</td>
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<td>nsSNP/Indels</td>
<td>6255</td>
<td>6752</td>
<td>6831</td>
<td>6217</td>
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<td>Novel</td>
<td>185</td>
<td>155</td>
<td>168</td>
<td>174</td>
<td>237</td>
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</table>
1972 - average age of death was 40 years in men and 50 years in women
- Aortic aneurysm accounted for 80% of deaths
- Stringent BP control (esp. losartan)
• Conventional sequencing of FBN not widely available due to gene size (65 exons, 257kb length)

• Diagnosis of OI typically clinical as well due to gene size/cost of conventional sequencing.
Sequencing in MFS/OI

• To investigate performance of massive parallel sequencing in these conditions 13 OI patients, 10 MFS with known COL or FBN mutations whole exome sequenced
  – All 13 OI mutations detected
  – 9/10 MFS mutations detected including
    • non-synonymous SNPs, small indels (<10bp), and a large UTR5/exon 1 deletion.
Phaeochromocytoma Paragangliomona Sequencing

- American College of Oncologists
  - genetic testing should be offered when *a priori* probability of a disease-associated mutation exceeds 10%
  - For phaeochromocytoma (PCC) and paraganglioma (PGL), the base rate of germline mutation is approximately 25%.

- Genetic testing has not been universally adopted for patients with PCC/PGL.
  - Why not?
    - large number of potential exons requiring sequencing, resulting in high costs.
      - *RET, NF1, VHL, SDHD, SDHB, SDHC, SDHA, SDHAF2, KIF1B, TMEM127, EGLN1* and *MAX*
      - *And two more since we published the paper!!! EPAS1 and FH*
  - A targeted sequential approach based on phenotype might limit costs, but
    - frequently results in significant delays in diagnosis.
    - As new genes are identified, panels are superceded.
Whole exome sequencing is an efficient and sensitive method for detection of germline mutations in patients with phaeochromocytomas and paragangliomas


*The University of Queensland Diamantina Institute, Translational Research Institute, Princess Alexandra Hospital, Woolloongabba, Brisbane, †Royal North Shore Hospital, The Kolling Institute, ‡University of Sydney, Sydney, NSW, §Department of Endocrinology, Royal Brisbane and Women’s Hospital, Brisbane and ¶UQ Centre for Clinical Research, The University of Queensland, Herston, Qld, Australia

Editor’s choice for January!

Next-generation sequencing for the genetic screening of phaeochromocytomas and paragangliomas: riding the new wave, but with caution*

Rodrigo A. Toledo* and Patricia L. M. Dahia*†
## Identified variants for 7 samples
(Illumina TruSeq™ Exome Enrichment Kit v2.0)

<table>
<thead>
<tr>
<th>Sample</th>
<th>No. of variants identified</th>
<th>No. of heterozygous variants in target genes*</th>
<th>No. of good quality** variants</th>
<th>No. of good quality coding or splice site variants</th>
<th>Identified mutation</th>
<th>Same as previously</th>
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<tbody>
<tr>
<td>PCC-10.3</td>
<td>45857</td>
<td>29</td>
<td>23</td>
<td>1</td>
<td>SDHD exon3 c.296delT p.Leu99ProfsX36</td>
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<tr>
<td>PCC-11.3</td>
<td>44402</td>
<td>19</td>
<td>16</td>
<td>1</td>
<td>SDHB exon2 c.137G&gt;A p.Arg46Gln</td>
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<td>PCC-12.3</td>
<td>43862</td>
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<td>21</td>
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<td>SDHC exon3 c.148C&gt;T p.Arg50Cys</td>
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<tr>
<td>PCC-13.3</td>
<td>42663</td>
<td>23</td>
<td>19</td>
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<td>SDHB exon7 c.689G&gt;A p.Arg230His</td>
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<tr>
<td>PCC-14.3</td>
<td>43881</td>
<td>17</td>
<td>14</td>
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<td>RET exon10 c.1832G&gt;A p.Cys611Tyr</td>
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<tr>
<td>PCC-15.3</td>
<td>42640</td>
<td>16</td>
<td>14</td>
<td>1</td>
<td>VHL exon2 c.481C&gt;T p.Arg161X</td>
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<tr>
<td>PCC-16.3</td>
<td>44635</td>
<td>17</td>
<td>13</td>
<td>0</td>
<td>None</td>
<td>No mutation identified using this capture platform</td>
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.....and 5 samples (Nimblegen SeqCap EZv3.0).

<table>
<thead>
<tr>
<th>Sample</th>
<th>No. of variants identified</th>
<th>No. of heterozygous variants in target genes*</th>
<th>No. of good quality** variants</th>
<th>No. of good quality coding or splice site variants</th>
<th>Identified mutation</th>
<th>Same as previously</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCC-16.3 (repeat)</td>
<td>34410</td>
<td>18</td>
<td>11</td>
<td>1</td>
<td>SDHC exon2 c.49delC p.Ala16fs</td>
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<tr>
<td>PCC-17.3</td>
<td>35411</td>
<td>14</td>
<td>11</td>
<td>1</td>
<td>SDHB exon5\ c.494_497delAAGG p.Glu165AlafsX39</td>
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<tr>
<td>PCC-18.3</td>
<td>35213</td>
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<td>17</td>
<td>1</td>
<td>VHL exon3 c.492G&gt;C p.Gln164His</td>
<td>Yes</td>
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<tr>
<td>PCC-19.3</td>
<td>33292</td>
<td>25</td>
<td>23</td>
<td>1</td>
<td>SDHD exon3 c.242C&gt;T p.Pro81Leu</td>
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<td>PCC-111.3</td>
<td>37564</td>
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<td>15</td>
<td>1</td>
<td>SDHC exon5 c.397C&gt;T p.Arg133X</td>
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</tr>
</tbody>
</table>
1972 - average age of death was 40 years in men and 50 years in women
- Aortic aneurysm accounted for 80% of deaths
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‘The genetics of common diseases: 10 million times as hard.’
Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The Wellcome Trust Case Control Consortium*
An explosion of discoveries
Common ‘polygenic’ diseases
• e.g. hypertension, diabetes, osteoporosis, many forms of arthritis
• Different individuals have different genetic variants in different, but overlapping, sets of genes
• Condition ‘runs in the family’ but transmission from generation to generation not so obvious.
# Heritability of Common Diseases

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>HERITABILITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANCERS</td>
<td></td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>25-56%</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>40%</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>42%</td>
</tr>
<tr>
<td>METABOLIC /VASCULAR DISEASES</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>30%</td>
</tr>
<tr>
<td>Stroke</td>
<td>32%</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>26%</td>
</tr>
<tr>
<td>AUTOIMMUNE DISEASES</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>55%</td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>88%</td>
</tr>
<tr>
<td>INFECTIOUS DISEASES</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>50-78%</td>
</tr>
<tr>
<td>Otitis Media</td>
<td>78%</td>
</tr>
</tbody>
</table>
Risk Prediction in Common Diseases

• Agreement that it is effective for
  – Type 1 diabetes
  – Alzheimer’s disease
  – Male coronary heart disease

• Several diseases it probably won’t work for in general population screening.

• Benefit likely to be greatest in combination with clinical findings/symptoms.
Risk Prediction in Common Diseases

• Agreement that it is effective for
  – Type 1 diabetes
  – Alzheimer’s disease
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• Several diseases it probably won’t work for in general population screening.

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Genetic Screening and Coeliac Disease

• Diagnosis currently is by antibody test followed by endoscopy
• Combined screening by antibody test, then gene test, then endoscopy
  – Reduces endoscopy requirement by 38% in women and 65% in men
  – saves >$600/case diagnosed
• Over 300,000 Australians have undiagnosed coeliac disease
  – >$180 million saving in screening costs.

Anderson et al, BMC Med, 2013
Whole Genome Sequencing - A New Microscope

LETTER

doi:10.1038/nature13394

Genome sequencing identifies major causes of severe intellectual disability

Christian Gilissen1*, Jayne Y. Hechir-Kwa1*, Djie Tjwan Thung1, Maartje van de Vorst1, Bregie W. M. van Bon1, Marjolein H. Willemsen1, Michael Kwint1, Irene M. Janssen1, Alexander Hoischen1, Annette Schenck1, Richard Leach7, Robert Klein2, Rick Tearle2, Tan Boi3, Rolph Pfundt1, Helger G. Yntema1, Bert B. A. de Vries1, Tjitske Kleefstra1, Han G. Brunner1,4*, Lisenka E. L. M. Vissers1* & Joris A. Veltman1,4*
Sequencing of major single gene inherited diseases should be universally available now.

Universal whole genome sequencing to predict risk of common diseases will likely occur within the next decade.
Personalised Medicine and Cancer

• Cancer sequencing: a frameshift in clinical practice
  – from treating patients according to the tissue of origin to treatment based on the molecular disorder caused by the driver DNA mutation.
  – better outcome prediction
  – better dosage optimisation and prediction of side-effects
  – earlier detection of relapse
  – development of new drugs.
Personalised Medicine and Cancer

• Gene mutations are the underlying mechanism causing cancers.
  — Identifying those mutations informs new treatment development.
  
  • Gleevec ‘Imatinib’ for chronic myeloid leukaemia.
Personalised Medicine and Cancer

• Sequencing can determine likelihood of resistance to chemotherapy.
  • Cetuximab and panitumumab in colorectal cancer – K-RAS mutations predict resistance.

Khambata-Ford S et al. JCO 2007;25:3230-3237
Cancer Treatment by Molecular Cause

- 2,890 pancreatic cancer diagnoses in Australia expected in 2014
- Treatment options are limited and life expectancy short.
Cancer Treatment by Molecular Cause

<table>
<thead>
<tr>
<th>Therapeutic</th>
<th>Proposed biomarkers</th>
<th>Estimated prevalence (%)</th>
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</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>High hENT1 expression</td>
<td>15</td>
</tr>
<tr>
<td>Platinums</td>
<td>BRCA2/PALB2 mutations</td>
<td>7</td>
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<tr>
<td>nab-Paclitaxel</td>
<td>SPARC expression</td>
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<tr>
<td>Erlotinib</td>
<td>KRAS wild type</td>
<td>7</td>
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<td>Irinotecan</td>
<td>Topoisomerase 1 overexpression</td>
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<tr>
<td>Trastuzumab</td>
<td>HER2 amplification</td>
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<tr>
<td>SMO inhibitors</td>
<td>PTCH mutations</td>
<td>2</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>CSF1R mutation</td>
<td>1</td>
</tr>
<tr>
<td>mTOR inhibitors</td>
<td>STK11/LKB1 mutation/loss</td>
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</tr>
</tbody>
</table>

- At least 47% of pancreatic cancers have mutations which are potentially targetable using existing medications.
**HER2 and Pancreatic Cancer**

- HER2 positive pancreatic tumours more likely to have brain and lung metastases, less likely to have liver metastases
  - Not just an innocent bystander
- HER2 amplification is a biomarker of response to herceptin in breast and gastric tumours
  - Suggests herceptin treatment may work for pancreatic cancer.

Chou et al, Genomic Medicine, 2013
Message

Sequencing of life threatening cancers should be universally available now.
UQ Centre for Clinical Genomics
UQ Centre for Clinical Genomics

- Over 1000 whole genomes and 3000 whole exomes sequenced since 2011.
- $12 million expansion planned in Q1 2015
  - Funded by UQ, UQDI, QUT, ACRF, PAH practitioners
  - Capable of >15,000 whole genomes per annum
  - Will be transformational for Qld cancer and heritable disease practice, and research.
PacBio RSII

• Advantages
  • Fast: runs 0.5-3 hours
  • Long reads: average 8.5 kb
  • No GC bias
  • Good detection of base modification

• Error rate?
  • Raw error rate 14%
  • Error is stochastic
  • 99.99% accuracy @ 10x
  • 99.9999% accuracy @ 20x

• Applications:
  • deNovo Assembly
  • Targeted sequencing
  • Base modification
  • Metagenomics
Problems with Genetic Testing

• Will require combinations of genetic tests, along with other known risk factors.
• Interpretation will be difficult
  – Problems already exist with single gene tests.
• May need to be validated in different populations and environments.
• What about diseases where there is no preventative treatment or benefit from early intervention?
• We are not ready for it yet!
  – Infrastructure
  – Reporting systems
  – Counseling network.
Government Responses

We are a new company set up by the Department of Health to help deliver the 100k Genome Project first announced by the Prime Minister David Cameron in December 2012.

This project will sequence the personal DNA code – known as a genome – of up to 100,000 patients over the next five years. This unrivalled knowledge will help doctors’ understanding, leading to better and earlier diagnosis and personalised care. Based on expert scientific advice, we will start by tackling cancer, rare diseases and infectious diseases.

The company will manage contracts for sequencing, data linkage and analysis, and set standards for patient consent.

“The UK will become the first ever country to introduce this technology in its mainstream health system.”

Genomics England was announced by Jeremy Hunt, Secretary of State for Health, as part of the NHS 65th birthday celebrations on 5 July 2013.

He said: “The NHS has a long track record as a leader in medical science advances and it must continue to push the boundaries by unlocking the power of DNA data.

“The UK will become the first ever country to introduce this technology in its mainstream health system – leading the global race for better tests, better drugs and above all better, more personalised care to save lives.

“Genomics England will provide the investment and leadership needed to dramatically increase the use of this technology and drive down costs.”

• New South Wales Government June 2014
  – Committed $24 million over four years to a medical genomics program led by Garvan Institute
  – Will enable rollout of whole genome sequencing for cancers and heritable diseases in NSW public hospitals.
Summary

• Genomics will change the practice of medicine radically over the next decade
  – Heritable diseases
  – Pharmacogenetics
  – Cancer
  – Infectious diseases.

• Personalised medicine is on our doorstep for rare and common diseases and cancers right now

• Australia needs to invest broadly in medical genomics to make the most of the potential clinical and research benefits of these changes.
Contact UQCCG

• General Enquiries:
  • Dr. Bruce Wyse (07) 3443 7020 b.wyse@uq.edu.au

• Project Enquiries:
  • Illumina NGS: Lisa Anderson lisa.anderson@uq.edu.au
  • PacBio NGS: Lawrie Wheeler l.wheeler@uq.edu.au
  • Microarray: Katie Cremin c.cremin@uq.edu.au