Genomic Medicine
How do we prepare Australia for this disruptive technology?

John Christodoulou
Chair of Genomic Medicine, Murdoch Children’s Research Institute and University of Melbourne
Melbourne, Australia

RACP Congress
9th May 2017
How Common are Genetic Disorders?

• ~20,000 genes (and then there is noncoding RNA…)
• over 7,000 known Mendelian disorders
• over 100 chromosomal syndromes
• 50% of the population during their lifetime
• 5% before the age of 25 yrs
• Up to 70% of tertiary paediatric centre admissions
• 28% of infant deaths
• 50% of miscarriages have a chromosomal abnormality
Traditional diagnostic approach for genetic disorders

- clinical evaluation
- biochemical screening tests
- targeted biochemical tests
- molecular karyotype (array CGH/SNP arrays)
- imaging studies
- biopsies – histology/EM
- functional studies – enzymology etc
- molecular genetic testing – one gene at a time

- prolonged, expensive and intrusive diagnostic odyssey
...enter next generation sequencing...
(aka massively parallel sequencing)

http://www.futuretimeline.net/blog/biology-medicine-blog.htm#.U1nYTV7yQds
Discovery of OXPHOS disease genes so far...

- mitochondrial respiratory chain disorders can affect any organ, and can have an onset at any age
- 1 in 5000 affected, very few effective treatments
- clinically, a very broad group of disorders, ~60% cases underlying genetic abnormality is unknown
- mutations occur in mitochondrial or nuclear DNA (~ 250 genes)

85 genes in last 7 years, a third of total

Number of disease genes identified

Alison Compton and David Thorburn, MCRI Melbourne
Genomics and cancer

- cancer is a disease of the genome
- all cancer involves somatic mutation
  - “driver mutations” – growth advantage
  - “passenger mutations” – pathogenesis
- rare somatic cancers
  - <6/10^5; collectively 22% of total
- germline cancers
  - 5-10% of all cancers; > 300 inherited cancer syndromes
- genomic molecular profiling
  - targeted therapies
  - germline cancers – inheritance, penetrance, genetic counselling
Genomic medicine in healthcare
WHAT COULD IT MEAN FOR THE PUBLIC?

• Faster diagnosis
• Improved prognosis
• Precise/targeted therapy – “precision medicine”
• Better manage disease risk
• Prevention

Australian Genomics Health Alliance
Melbourne Genomics Health Alliance
DEMONSTRATION PROJECT 2014 – 2015

• Establishing state-wide platform for genomic information
• Developed prototype system
  • multiple organisations & different conditions
• Evaluate prototype compared to standard care
  • what worked, what didn’t, potential solutions,
  • detection rate, change in management, cost effectiveness
• Shared approaches

Approach:
• Prospective recruitment (n=315 patients)
• Whole exome sequencing
• Targeted analysis
• In parallel with usual investigations
Shared approaches

- Common clinical consent form (germline)
- Data standards
- Curation guidelines
- Common informatics pipeline
- Common report format
- Multidisciplinary review meetings
# Genomics in Action

## CHILDHOOD SYNDROMES CASE STUDY

**Childhood syndromes** - 80 children, RCH Melbourne

Patients received both:

- **A. Traditional diagnostic tests** (eg MRI, muscle biopsy)
- **B. Whole exome sequencing** (Genomics)

<table>
<thead>
<tr>
<th>Experimental finding</th>
<th>Traditional Diagnostics</th>
<th>Whole Exome Sequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of diagnosis</td>
<td>11%</td>
<td>55%</td>
</tr>
<tr>
<td>Average cost per patient</td>
<td>$27,040</td>
<td>$6,003</td>
</tr>
<tr>
<td>Patients with improved care outcomes</td>
<td>4%</td>
<td>16%</td>
</tr>
</tbody>
</table>

*Stark Z, et al Genetics in Medicine 2016:18; 1090 - 1096*
$25M NHMRC Targeted Call for Research 2016-2020

- Demonstrate how Australians can benefit through the use of genomic data in one or more diseases.

- Provide evidence on the cost effectiveness of implementing genomics into the Australian health system.

- Provide practical strategies that can be used by Australian health system planners and policymakers to integrate genomic medicine into healthcare.

- Build Australia’s research expertise in genomics.
A national approach

CHALLENGES & THREATS

- Duplication between states
- Inequity of access for patients
- Preparing a genomic workforce
- Lack of data storage/difficulty in sharing data
- Inactivity, fragmentation, internal competition
- No common ethics, or consent forms
- Divide between state and federal health systems
A national approach

STRENGTHS & OPPORTUNITIES

- Perfect time for collaboration
- NATA accredited facilities in all states
- Linkage nationally & internationally
- Quality & capability of clinical & research networks
- National healthcare system = equity of access
- High degree of genomic activity in Australian research

Australian Genomics Health Alliance
AGHA aims to demonstrate the cost effectiveness, diagnostic efficacy and impact on clinical care of genomic medicine
Australian Genomics
MORE THAN 60 PARTNERS, 200+ INVESTIGATORS

PARTNERS

Harry Perkins Institute of Medical Research
Path West
Genetic Services of Western Australia
Princess Margaret Hospital
Telethon Kids Institute
Royal Perth Hospital
Sir Charles Gairdner Hospital
University of Western Australia

South Australian Health & Medical Research Institute
SA Pathology / Centre for Cancer Biology
Women's and Children's Hospital
University of Adelaide
Royal Adelaide Hospital

Melbourne Genomics Health Alliance
Monash University
Monash Medical Centre
Victorian Comprehensive Cancer Centre
The Florey Institute of Neuroscience and Mental Health

Royal Hobart Hospital

The University of Queensland
Lady Cilento Children's Hospital
Institute for Molecular Bioscience
QIMR Berghofer Medical Research Institute
Wesley Hospital
Royal Brisbane and Women's Hospital
Princess Alexandra Hospital
Diamantina Institute
Pathology Queensland
Queensland University of Technology
Queensland Genomics Health Alliance

Sydney Children's Hospitals Network
Royal North Shore Hospital
Garvan Institute of Medical Research & KCCG
Kinghorn Cancer Centre
NSW Health Pathology
Children's Cancer Institute Australia
The University of Sydney
Children's Medical Research Institute
University of New South Wales
Centre for Genetics Education
AIHI / Macquarie University

Australian National University
Murdoch Children's Research Institute
Victorian Clinical Genetics Services
Melbourne Health / Royal Melbourne Hospital
The University of Melbourne
Walter and Eliza Hall Institute of Medical Research
Peter MacCallum Cancer Centre
Royal Children's Hospital
Victorian Life Sciences Computation Initiative
Austin Hospital
Infrastructural change through:
RESEARCH PROGRAMS & EXEMPLAR FLAGSHIPS

Program 1
A National Diagnostic and Research Network
Developing the best diagnostic approach for each disease area

Program 2
A National Approach to Data Federation and Analysis
Linking genomic and clinical data

Program 3
Economics, Implementation Science and Health Policy
Health economics, policy development, implementation science & communication

Program 4
Genomics Workforce, Education and Ethics
Mapping education & training needs, addressing ethical implications of genomic medicine

Rare Disease Flagship
Existing Activities

Cancer Flagship
Clinically driven Patient focused Enabling research

Clinical Outcomes
Prevention  Early Diagnosis  Early Intervention  Surveillance  Targeted Intervention or Therapy

Analysis  To provide a strong ethically informed evidence base for applying genomics to clinical practice

Policy  Practical strategies to inform Australian Health system planners and policy makers
A National Diagnostic and Research Network
PROGRAM ONE

• Program One is comprised of expert clinicians, diagnosticians and researchers from across Australia

• Delivery of a **coordinated and sustainable system** for the provision of genomic testing in the clinical environment – technology agnostic.

• **Evidence** to support funding as part of clinical care.

• **National referral network** with standardised approach to diagnosis.

• **Unified approach** to test ordering, minimal clinical dataset required, ethics, consent.

**Secondary aim:** identification of “enriched” cohorts of patient for gene discovery research projects.
A National Diagnostic and Research Network

PROGRAM ONE

• Three important initiatives

National Consent - develop guidelines for national consent for clinical genomic testing

Variant Re-Classification - guideline development, processes for review & re-classification & processes for notification of re-classification
  • major state jurisdictional issues relating to privacy & data sharing

MSAC Applications - development of future MSAC applications for diseases that have the required clinical and cost utility data

Program One pilots systems, develops recommendations embedded in clinical centres and drives health system change
Aim: Integrating with our Programs to drive research into the nationwide implementation of genomic testing

Each specific flagship is underpinned by:
- Strong existing national and international clinical, diagnostic and research partnerships
- Demonstrable leverage with other programs

Aim to establish a virtuous cycle of rapid translation and implementation between clinicians and researchers to evaluate pathogenicity, gene discovery and the development of innovative diagnostic tools.
First two years:

- **Neuromuscular disorders** (Lead: Nigel Laing, UWA)
- **Mitochondrial disorders** (Leads: David Thorburn, John Christodoulou, MCRI)
- **Neurodevelopmental disorders** (Lead: Jozef Gecz, UA)
- **Genetic immune disorders** (Lead: Matthew Cook, ANU)
- **Renal disorders** (Andrew Mallett, QLD Renal Genetics/KidGen collaborative)

Second round of Flagships (2018/2019)
EOI open mid 2017
Impact of Genomics on Cancer Surveillance and Therapy

**ALL Treatment**
- **Lead:** Deborah White, SAHMRI
- **RNA-Seq** with historical cohorts as a comparator
- Leveraged off REGALLIA study

**Clinical Gene Panels for Treatment**
- **Lead:** Stephen Fox, PMCC
- **Cancer Super Panel** compared to standard care, matched somatic and germline analysis
- Combined Melbourne Genomics and Australian Genomics Flagship

**Manage Patient Risk (germline)**
- **Leads:** David Thomas, Garvan & Robyn Ward, UQ
- **Whole Genome Sequencing** with targeted analysis
- Leverages ICONN, Garvan AYA cohort, CCIA PMP and Westmead cohort
A National Approach to Data Federation and Analysis
PROGRAM TWO

1. Clinical variant classification
   - Surveying current practice around Australia
   - Guidelines to foster sharing and consistency of reportable variant calls

2. Genotype/Phenotype national data resources
   - Establishing a framework for capturing phenotype-genetic variant associations
   - Patient Archive (Tudor Groza – Garvan Institute)

3. Accurate Phenotype information
   - A canonical reference ontology for phenotypic information
   - Linking with standards developed internationally and expanded locally in CSIRO
   - e-health infrastructure (working with ADHA)
4. Common framework for pipelines

- Mapping the diverse bioinformatic methods across the Nation
- Developing a framework for quality control, performance assessment and description of pipelines

5. Data Sharing and Archiving

- Developing the legislative and data governance landscape within Australia to allow aggregation of clinical genomic data
- Building nationalised infrastructure to allow the ethical sharing, querying and archiving of standardised clinical genomic data

Program Two pilots the architecture and evaluates the governance for a FEDERATED REPOSITORY of re-identifiable genomic / phenotypic data. The aim is to support data interrogation and sharing for clinical benefit and to preserve of data security for the patient.
Economic analysis, Implementation Science & Policy

**PROGRAM 3**

- **Health Economics**
- Hospital Data
- Recruited Patient Surveys and Data Collection
- Cost effectiveness modelling
- Data analysis and contribution to MSAC applications

- **Policy Development**
  - Landscape analysis of frameworks used to evaluate decisions around genomic testing, including reimbursement

- **Implementation Science**
  - Explores and overcomes the barriers for adoption of research findings
  - Promote uptake of genomics into routine healthcare in clinical, organisational and policy contexts
Workforce, Education & Ethics

PROGRAM 4

• Seeks to **understand the education and training needs** of those whose role will be impacted by clinical genomics.

• Mapping current education and training activities available to Australian professionals working in genomics.

• Identifying **future education needs** of health professionals.

• Investigating the **psychosocial implications** of genomic testing with patients and families.

• Conducting **ethical analyses of clinical genomics**, such as data sharing, uncertainty, incidental findings and models of consent.
Linkages
INTERNATIONAL & GLOBAL INITIATIVES

GA4GH
Baylor College of Medicine
G2MC
Australian Genomics Health Alliance
Broad Institute
Genomics England
UCL Great Ormond Street Institute of Child Health
• So where are we in the Gartner hype cycle??

Visibility

Peak of inflated expectations

Plateau of productivity

Slope of enlightenment

Trough of disillusionment

Technology trigger

Time
AGHA - overall strategy

• **Act locally**
  • target developments embedded within the disparate systems of state health departments, leveraging existing infrastructure, collaborations and local networks

• **Build nationally**
  • Expand upon pilot projects established in QLD, NSW, and VIC; Link around the country leveraging the clinical and diagnostic network of the AGHA

• **Link internationally**
  • Harness existing international collaborations to ensure the solutions and systems we pilot in Australia take advantage of technologies, practices and principles at the forefront of international best practice
Questions?

Stay in touch with us:

• E: australian.genomics@mcri.edu.au
• W: australiangenomics.org.au
AGHA engagement
COMMUNITY ADVISORY GROUP

Richard Vines, CEO Rare Cancers Australia (Chair)
Hayley Andersen, CEO Melanoma Australia
John Cannings, Partner PWC & Patient representative
Sean Murray, CEO Australian Mitochondrial Disease Foundation
Jessica Bean, Rare Disease Patient representative (& Advocate)
Mikaela Straface, CEO Kidney Health Australia (TBC)
Martin Delatycki, AGHA Academic representative
Demonstration projects

The **Beacon Project** is an open web service that tests the willingness of international sites to share genetic data. It is being implemented on the websites of the world’s top genomic research organizations.

**Matchmaker Exchange** is a federated network of databases whose goal is to find genetic causes of rare diseases by matching similar phenotypic and genotypic profiles.

The **BRCA Exchange (Challenge)** aims to advance understanding of the genetic basis of breast cancer and other cancers by pooling data on BRCA genetic variants from around the world, bringing together information on sequence variation, phenotype and scientific evidence.

The **Cancer Gene Trust** proposes to aggregate somatic cancer mutation data and clinical data in order to enable greater personalized clinical care for individuals with rare cancer mutations.
Neuromuscular disorders

- **Lead:** Prof Nigel Laing, University of Western Australia, WA
- **Approach:** Comparing current clinically-funded genomic screening: large panels and exomes (WES) with whole genome sequencing (WGS).
- **Functional Genomics:** Aligned with model organism research groups: zebra fish (MU & ARMI) and mice (MCRI).
- **Patient recruitment sites:** WA, NSW, QLD, VIC, SA (paed & adult)
Mitochondrial disorders

• **Leads:** Prof David Thorburn, Prof John Christodoulou, MCRI, VIC

• **Approach:** Half receiving WGS, half WES+mtDNA to develop a comprehensive comparison of the technologies.

• **Patient recruitment** in WA, NSW, QLD, VIC, SA (adult and paed)

**Functional Genomics:** Aligned with cell line and mouse model research groups (MCRI and MU).
Renal disorders

- **Lead:** Dr Andrew Mallett, QLD Renal Genetics, KidGen Collaborative lead, Royal Brisbane and Women’s Hospital, QLD
- **Approach:** Comparing clinically-funded panels with WES
- Well-established (and expanding) collaborative model
- Patient recruitment in QLD, NSW, WA, SA, VIC and TAS (adult & paed)
- **Functional genomics:** Aligned with Kidney Development, Disease and Regeneration research group (MCRI)
Neurodevelopmental disorders

Lead: Prof Jozef Gecz, University of Adelaide

1. Brain Malformations and Leukodystrophies
   - **Leads:** Rick Leventer, RCH and Paul Lockhart, MCRI, VIC
   - Approach: Whole exome sequencing
   - Recruitment in WA, NSW, QLD, VIC, SA, NT (paed)

2. Epileptic Encephalopathies
   - **Lead:** Ingrid Scheffer, University of Melbourne, VIC
   - Approach: Whole exome sequencing
   - Recruitment in WA, NSW, QLD, VIC, SA, TAS (paed)
   - *EE and Brain malformations aligned with model organism research groups (Flies CP-US, C. elegans (MU), mice (HPIMR).*
3. Intellectual Disability

- **Leads:** Tony Roscioli, The Garvan & Mike Field, Hunter Genetics, NSW
- Approach: Whole genome sequencing
- Planned roll out in 2017
- Recruiting in WA, NSW, QLD, VIC, SA (paed)
Genetic immune disorders

Lead: Prof Matthew Cook, Australian National University

- **Approach:** Whole genome sequencing
- Well-established (and expanding) collaborative model
- Patient recruitment in NSW, VIC and ACT (adult & paed)
- **Functional genomics:** Aligned with mouse model research group (WEHI) and immune cell research group (ANU)
## Rare Disease Flagships

**SUMMARY OF PATIENT RECRUITMENT SITES & NUMBERS**

<table>
<thead>
<tr>
<th>RARE DISEASE FLAGSHIP</th>
<th>STATES</th>
<th>RECRUITMENT</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuromuscular Disorders</td>
<td>WA, NSW, QLD, VIC, SA</td>
<td>200 A / 320 P</td>
<td>520</td>
</tr>
<tr>
<td>Mitochondrial Disorders</td>
<td>WA, NSW, QLD, VIC, SA</td>
<td>110 A / 100 P</td>
<td>210</td>
</tr>
<tr>
<td>Epileptic Encephalopathy</td>
<td>WA, NSW, QLD, VIC, SA, TAS</td>
<td>65 P</td>
<td>65</td>
</tr>
<tr>
<td>Brain Malformations and Leukodystrophies</td>
<td>WA, NSW, QLD, VIC, SA, NT</td>
<td>225 P</td>
<td>225</td>
</tr>
<tr>
<td>KidGen Renal Genetics</td>
<td>WA, NSW, QLD, VIC, SA, TAS</td>
<td>357 A / 163 P</td>
<td>520</td>
</tr>
<tr>
<td>Genetic Immunology</td>
<td>ACT, NSW, VIC</td>
<td>150 A / 180 P</td>
<td>330</td>
</tr>
<tr>
<td>Intellectual Disability</td>
<td>WA, NSW, QLD, VIC, SA</td>
<td>400 P</td>
<td>400</td>
</tr>
<tr>
<td><strong>TOTAL FIRST ROUND RD FLAGSHIPS</strong></td>
<td></td>
<td><strong>2270</strong></td>
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</table>
Disease Flagship
CANCER

Impact of Genomics on Cancer Surveillance and Therapy

**ALL Treatment** (Lead: Deborah White, SAHMRI)
- **RNAseq** with historical cohorts as a comparator
- Leveraged off REGALLIA study
- Recruiting in SA, NSW, VIC, QLD ~ 80 – 100 per annum x 5 years

**Clinical Gene Panels for Treatment** (Lead: Stephen Fox, PMCC)
- **Cancer Super Panel** compared to standard care, matched somatic and germline analysis
- Combined Melbourne Genomics and Australian Genomics Flagship
- Recruiting in VIC, NSW, QLD, WA ~400 patients over two years
**Manage Patient Risk (germline) - AYA/Paed** (Lead: David Thomas)
- **Whole Genome Sequencing** with targeted analysis
- Recruiting from NSW primarily, others through ACC
- ~1400 patients over five years

**Manage Patient Risk (germline) - ICCon** (Lead: Robyn Ward, UQ)
- **Whole Genome Sequencing** with targeted analysis
- Leverages ICONN, Garvan AYA cohort, CCIA PMP and Westmead cohort
- 15 FCCs: WA, SA, QLD, NSW, VIC, TAS, ACT.
- ~300 patients over five years
Rare Disease Flagships
AG HA PATIENT RECRUITMENT SITES

PARTNERS

Harry Perkins Institute of Medical Research
Path West
Genetic Services of Western Australia
Princess Margaret Hospital
Telethon Kids Institute
Royal Perth Hospital
Sir Charles Gairdner Hospital
University of Western Australia
South Australian Health & Medical Research Institute
SA Pathology / Centre for Cancer Biology
Women's and Children's Hospital
University of Adelaide
Royal Adelaide Hospital

Peak Professional Bodies
Royal College of Pathologists of Australasia
Human Genetics Society of Australasia

National Partners
Bioplatforms Australia
Australian Genome Research Facility
BioGrid Australia
National Computational Infrastructure
CSIRO
Rare Voices Australia
Rare Cancers Australia
Australian Mitochondrial Disease Foundation

International Partners
Broad Institute of MIT and Harvard
Baylor College of Medicine
UCL Great Ormond St Institute of Child Health
Global Alliance for Genomics and Health
Global Genomic Medicine Collaborative
Genomics England

The University of Queensland
Lady Cilento Children's Hospital
Institute for Molecular Bioscience
QIMR Berghofer Medical Research Institute
Wesley Hospital
Royal Brisbane and Women's Hospital
Princess Alexandra Hospital
Diamantina Institute
Pathology Queensland
Queensland University of Technology
Queensland Genomics Health Alliance
Sydney Children's Hospitals Network
Royal North Shore Hospital
Garvan Institute of Medical Research & KCCG
Kinghorn Cancer Centre
NSW Health Pathology
Children's Cancer Institute Australia
The University of Sydney
Children's Medical Research Institute
University of New South Wales
Centre for Genetics Education
AIHI / Macquarie University
Australian National University
Murdoch Childrens Research Institute
Victorian Clinical Genetics Services
Melbourne Health / Royal Melbourne Hospital
The University of Melbourne
Walter and Eliza Hall Institute of Medical Research
Peter MacCallum Cancer Centre
Royal Children's Hospital
Victorian Life Sciences Computation Initiative
Austin Hospital
Australian Genomics Health Alliance
Rare Disease Flagships
FLAGSHIP MODEL: CONSENT PROCESS

- **National approach:** Genetic Counsellors (GC) appointed in each state (NSW, VIC, WA (TBD), SA, QLD). GC’s part of multi-disciplinary teams (flagship clinician, project officers, lab scientists and variant curator).

- **Work with flagship clinician to discuss suitability/eligibility of patient to be enrolled in study**

- **STUDY CONTACT 1**
  Consent process with patient and family
  (discussion of genomic testing, possible results, use of participant data, health economic survey, patient experience survey, and potential for flow-on research)

- **STUDY CONTACT 2**
  Return of results & discussion of implications, and/or action plan for further research

- **Support collection of clinical data**
  (including family history) & clinical data entry into clinical database

- **STUDY CONTACT 3**
  Survey patient/parent experience (6 months post) & collection of medical record data

- **STUDY CONTACT 4**
  Administer 12month follow up health economic survey

Australian Genomics Health Alliance
Patient Pathway beyond recruitment
EXOME SPECIFIC

1. Exome testing
2. MDT
3. Results returned
4. Clinical follow-up
5. Research Pipeline
The Australian Health Data Paradox

- The full potential is gleaned through sharing of genomic and associated phenotypic data
- Existing data governance and privacy laws preclude this sharing
- Undermines Australia’s capacity to benefit fully from the genomics revolution in healthcare
- SOLUTION:
  - Federation of clinical/genomic data sets
  - Bringing analysis to the data
  - Tease out the-use of genomic data for clinical or research purposes

IDEAL: Appropriate use of identified data, accessibility of re-identifiable data
Appropriate use of identified data accessibility of re-identifiable data

CLINICAL DATA & GENOMIC HEALTH DATA can be viewed similarly:
• held in fragmented repositories in hospitals, clinics, laboratories
• governed by similar legal, social and ethical issues
• with incredible potential clinical benefit to sharing co-existing with a tension to preserve patient confidentiality and privacy

STATE HEALTH DEPARTMENTS are the starting point: but the size and complexity of the data is beyond the current resources and infrastructure of the states

DATA IS AN ISSUE OF STORAGE and SHARING

<table>
<thead>
<tr>
<th>CLINICAL DATA</th>
<th>STORED SEPARATELY</th>
<th>GENOMIC DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>MyHealthRecord</td>
<td>BUT SECURELY LINKED</td>
<td>State-based repositories</td>
</tr>
</tbody>
</table>

CONSENT for re-identifiable genotype-phenotype information to be Shared nationally and internationally
Program Two
PATIENT ARCHIVE / MATCHMAKER EXCHANGE

Networked nationally, and linked internationally
beacon.australiangenomics.org.au
mme.australiangenomics.org.au