Genomics and Healthcare
A local and global perspective

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Director, Victorian Clinical Genetics Service
David Danks Professor of Child Health Research,
University of Melbourne
The opportunity and the challenge

We now have the ability to generate large amounts of genomic information at relatively low cost

- More rapid path to diagnosis
- Increased emphasis on prevention, early intervention
- Increase in therapies targeted to the individual

Realizing genuine benefits from advances in genomic technology requires a transformation in how we deliver healthcare
Current limitations

- Slow translation of research into new diagnostic tests
- Inequities in access to tests
- Lack of infrastructure to support ‘bedside to bench’
- Poor ‘whole of life’ care small, fragmented efforts

Whole of system change is needed

- the Workforce
- the Laboratory
- Data storage & linkage
- in Clinical practice
Genomics and Healthcare
A local and global perspective

- Melbourne Genomics Health Alliance
- The Global Alliance for Genomics and Health
Melbourne Genomics Health Alliance
Five Year Vision

Excel in the use of genomics to tailor health care

Clinically driven

Shared & collaborative

Clinical genomes available for research use
Demonstration project

To be completed in first 12 months

Prototype crawler, US coast guard
Demonstration Project- 12 months!!

Prospective: WES with targeted analysis in parallel with usual investigations

Evaluation: (1) **Process**: barriers, issues, requirements

(2) **Performance**: diagnosis, cost, time

(3) **Threshold analysis**: conditions for financial viability

(4) **Health economic analysis**

\[ n= 200 \text{ patients} \]
One assay – lifelong selective analysis

70 CMT genes
130 Epilepsy genes
20 hCRC genes
2500 CS genes

Gene discovery
Health risk research
Predictive panel
Therapeutic response

THE UNIVERSITY OF MELBOURNE
agrf
Murdoch Childrens Research Institute
Walter+Eliza Hall Institute of Medical Research
CSIRO
The Royal Melbourne Hospital
The Royal Melbourne Hospital
PATIENT EXPERIENCE

- Patient presents
- Eligible
  - Consent & test sample
    - Survey
    - Result return (Study Investigator and/or Research GC)
      - Survey
      - +/- Verification
- Usual care

LABORATORY

- DNA extraction and sequencing
  - NATA lab
  - common pipeline
  - filtered for relevant genes
- Technical report
  - Multidisciplinary review of variants
- Research report clinically significant variants
Established clinically-led whole of system prototype

Patient engagement
- Genetic counselling
- Consent
- E-access
- Patient enters lifestyle and socio-economic data

Community Advisory Group

Clinician involvement
- Gene lists
- Recruitment criteria
- Multidisciplinary review
- eView
- Result report format
- Pipeline development
Ensured benefits for research

Researchers within the Alliance have access to
• Common bioinformatics pipeline
• Exome data (FASTQ, BAM, VCF) - RDSI
• Other collateral (e.g. databases, PICFs)
• (patient entered data, clinical data)
Research

Original
Unstable
Bespoke

Clinical

Proven
Predictable
Standardised

Adapted from Graham Taylor
Needs from many aspects

Clinicians
Patients
Ethics
Pathology
IT
Geneticists
Diagnostics
Bioinformaticians
Databases
Programmers
Sequencing Laboratories
Hospitals
IP

Demonstration Project
Genomics and Bioinformatics Advisory Group

- Hospitals
- Conditions
- Sequencing laboratories
- Exomes

Standard input

Map

Call variants

Annotate

Prioritise and filter

Germline and somatic single exomes

Targeted analysis by condition
Exclusion list (ACMG etc)

RefSeq CCDS gene annotations

Manageable output

Adapted from Natalie Thorne
Biinformatics Pipeline

Test case (exome) with known disease-causing variant

**Exomiser** ranked the variant 477 despite giving it the condition name

**Ingenuity, Extasy** also poorly ranked

In our pipeline, the true variant ranked 1st

Cornelia de Lange Syndrome
<table>
<thead>
<tr>
<th>CEO’s</th>
<th>Gareth Goodier</th>
<th>Doug Hilton</th>
<th>Stephen Smith</th>
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<tbody>
<tr>
<td></td>
<td>Kathryn North</td>
<td>Lynne Cobiac</td>
<td>Christine Kilpatrick</td>
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<tr>
<th>Steering Group</th>
<th>Clara Gaff (program leader)</th>
<th>Julian Clark</th>
<th>Mike South</th>
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<tr>
<td></td>
<td>James Angus (chair)</td>
<td>Paul Waring</td>
<td>Ingrid Winship</td>
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<td>Andrew Sinclair</td>
<td>Trevor Lockett</td>
<td>Sue Forrest</td>
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<tr>
<th>Project Team</th>
<th>Ivan Macciocca (clinical)</th>
<th>Tim Bakker (IM)</th>
<th>Gemma Brett (RGC)</th>
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<tr>
<td></td>
<td>Natalie Thorne (bioinf)</td>
<td>Michele Cook (admin)</td>
<td>Ella Wilkins (RGC)</td>
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<tr>
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<th>CMT</th>
<th>CS</th>
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<td>Clinical Interpretation and Reporting</td>
<td>Community</td>
<td>Information Management</td>
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<th>Technical Expertise</th>
<th>Pipeline platform</th>
<th>Variant database</th>
<th>Clin-Bioinf workforce</th>
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<th>Education</th>
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<td>IM/IT</td>
<td>Business Case</td>
<td>Evaluation</td>
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Systems operational

Common Bioinformatics Pipeline

Variant Curation Database

Multidisciplinary review (16)

Bioinformatics and Genomics Advisory group
Co-Chairs - Alicia Oshlack, Graham Taylor

Agreed (draft) standards, guidelines, templates

Clinical Interpretation and Reporting advisory group
Chair: Paul James
Acknowledgements

STEERING GROUP
Jim Angus
Andrew Sinclair
Paul Ekert
Ingrid Winship
Paul Waring
Sue Forrest
Mike South
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Monique Ryan
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Terry Brennan
Fernando Martin Sanchez
Wayne Mather
Emeline Ramos
Genomics and Healthcare
A local and **global** perspective

- Melbourne Genomics Health Alliance
- The Global Alliance for Genomics and Health
The international challenge

Right now:
  - Data is typically in silos: by type, by disease, by institution
  - Analysis methods are non-standardized, few at scale
  - Approaches to regulation, consent and data sharing

If we don’t act: risk a hodge-podge of Balkanized data, such as electronic medical records in the USA
Mission

To accelerate progress in human health by helping to establish a common framework of harmonized approaches to enable effective and responsible sharing of genomic and clinical data, and by catalyzing data sharing projects that drive and demonstrate the value of data sharing.
A fast paced non-profit start-up…

January 2013: 50 people from eight countries met in NYC to define the problem and consider solutions

June 2013: after having engaged 80 people in writing White Paper, we announced the formation of the Alliance with 70 organizations as Partners to take on the challenge

December 2013: four Working Groups up and running; Expanded Steering Committee; Executive Staff at Host Organizations; Progress on governance, branding…

March 2014: Launch at Wellcome Trust in UK

October 2014: Meeting in San Diego as satellite to ASHG
# Partner overview

<table>
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<tr>
<th>220</th>
<th>25</th>
<th>6</th>
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<tr>
<td><strong>Number of partner organizations</strong></td>
<td><strong>Number of countries in which alliance partners are based:</strong></td>
<td><strong>Number of continents in which alliance partners are active:</strong></td>
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<tr>
<td>Includes a wide variety of groups: Research Institutes, Academic Medical Centers, Universities, Disease Advocacy Organizations and Patient Groups, Funders, Life Science and Information Technology Companies, and more</td>
<td>Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Finland, France, Germany, Hungary, India, Ireland, Japan, Mexico, Netherlands, New Zealand, Singapore, Spain, South Africa, Sri Lanka, Sweden, Switzerland, United Kingdom, United States.</td>
<td>Active throughout the globe, with a presence in 6 continents: Africa, Asia, Australia, Europe, and North and South America</td>
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Working Groups, working model

Iterative process based on urgency, consultation, revision

• Effective (small) Working Groups, active membership
• Prepare project tools and Code of Conduct, distribute broadly for comment
• Take comments on-board, iterate and advance work
• Distribute initial work product, ask for comment
• Final work product at discretion of Working Group
• Steering Committee sign-off on process and content

Modeled on the World Wide Web Consortium (W3C)
Working Group current projects

**Regulatory and Ethics:** International Code of Conduct for Genomic and Clinical Data Sharing; Preparation of generic consent clauses; Ethics review Safe Harbor and data safe havens

**Data:** Governance of and updates to standard file formats; Development of machine-readable interfaces (APIs) to enable exchange of variation in genome sequences across groups

**Security:** Security framework development including specification of technical standards

**Clinical:** Broad assessment of methods for disease phenotyping; Development of a matchmaking toolbox (genotype and phenotype) to enable gene discovery
Related Initiatives – CWG Task Teams

**BRCA Challenge**
This project will identify and involve groups internationally who have datasets on specific genes of interest. We will aim to pool data on variants from current sequencing efforts, coupled with phenotype data, as an international data sharing resource to improve identification of clinically actionable variants.

**Catalogue of Activities**
In line with Clinical Working Group's desire to not reinvent the wheel and learn from existing endeavours, the group has created a catalogue of current activities related to data sharing to be used as a resource for researchers and clinicians. The Work Product will include a list of specific activities for a given topic area with a brief description, website information and contact information compiled for each activity.

**Clinical Cancer Genome**
The Clinical Cancer Genome Task Team is striving to harmonize the clinical sequencing efforts in the global cancer community. It hopes to highlight existing efforts that are interoperable or moving towards sharing of data. Ultimately, this group hopes to promote outcomes via standards and best practices that support clinical decision-making.

**eHealth**
The goal of this Task Team is to determine what current efforts exists in eHealth that attempt to collect and link genomic and phenomic data. The hope is to showcase these efforts in a manner that promotes awareness and learning from best practices as well as, where possible, harmonize efforts and

**Matchmaker Exchange**
This project will allow researchers and clinicians working in both germline and cancer to discover samples with a given rare genotype or phenotype. In order to, the CWG will facilitate and help create an interoperable solution.

**Phenotype Ontologies**
This project aims to bring together existing international efforts to develop and promote standardized language and tools for recording patient clinical phenotypes.
Progress made in 2014

BRCA Challenge

• Leadership: Sir John Burn (University of Newcastle) and Stephen Chanock (NCI)
• International Steering Committee established

MISSION: To aggregate BRCA1 and BRCA2 data to support highly collaborative research activities that will generate the most informed understanding of BRCA variation and its impact on human health.

• Short term – consolidate large datasets through submission to existing public BRCA databases (e.g. ClinVar, LOVD, UMD)
• Longer term – expand data sources, expert classification of variants, and functional studies, etc

Create a model approach for GA4GH to use for other disease areas of study
Progress made in 2014

**Matchmaker Exchange**

**The Challenge:**
- >60% of exome sequencing cases unsolved
- Case data sits in isolated databases.
- Phenotypic data is underrepresented in most genomic datasets

**The Solution:**
A federated platform *(Exchange)* to facilitate the matching of cases with similar phenotypic and genotypic profiles *(Matchmaking)* through application programming interfaces (APIs)
Realising genuine benefits from advances in genomic technology requires a transformation in how we deliver healthcare:

- More rapid path to diagnosis
- Increased emphasis on prevention, early intervention
- Increase in therapies targeted to the individual
- National approach to improve equity of access and avoid duplication
- “Critical mass” needed in specific areas – centres of excellence

A decade of major genomic technological advances progressing faster than “Moore’s Law”
What next?
National Genomics Healthcare Initiative

- WA Health
- University of Western Australia
- Harry Perkins Institute

- SA Pathology
- SA Health & Medical Research Institute

- University of Melbourne
- AGRF
- CSIRO

- Genetic Health Qld
- University of Queensland

- Sydney Children’s Hospital Network
  Garvan Institute of Medical Research
  Children’s Cancer Institute Australia

- Melbourne Children’s (MCRI, RCH, VCGS)
  Walter + Eliza Hall Institute
  Royal Melbourne Hospital
  Peter MacCallum Cancer Centre
Common challenges requiring a national approach

- Hardware/Storage
- Expertise/Education
- Health economics
- Workforce
- Policy

- Common challenges
- Sharing of best practice
- Reduce duplication
“We finished the genomic map, now we can't figure out how to fold it.”