What can genomics offer to those with rare genetic disorders?

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- 27th November 2018

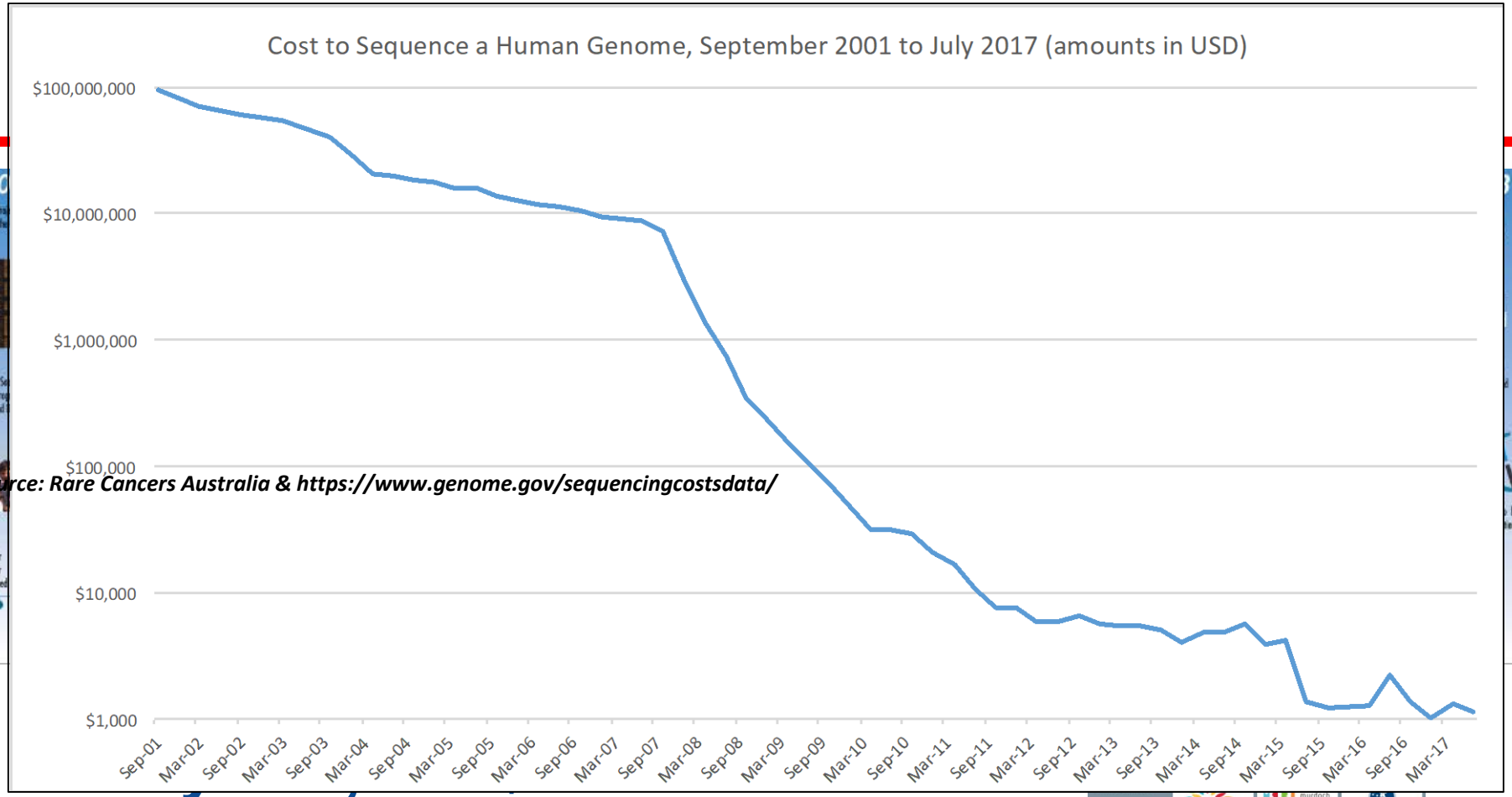
Summary of presentation

- setting the scene
- the promise of genomic medicine
- can genomic medicine be delivered at a national level?
- technical challenges on the horizon

Traditional diagnostic approach for suspected 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

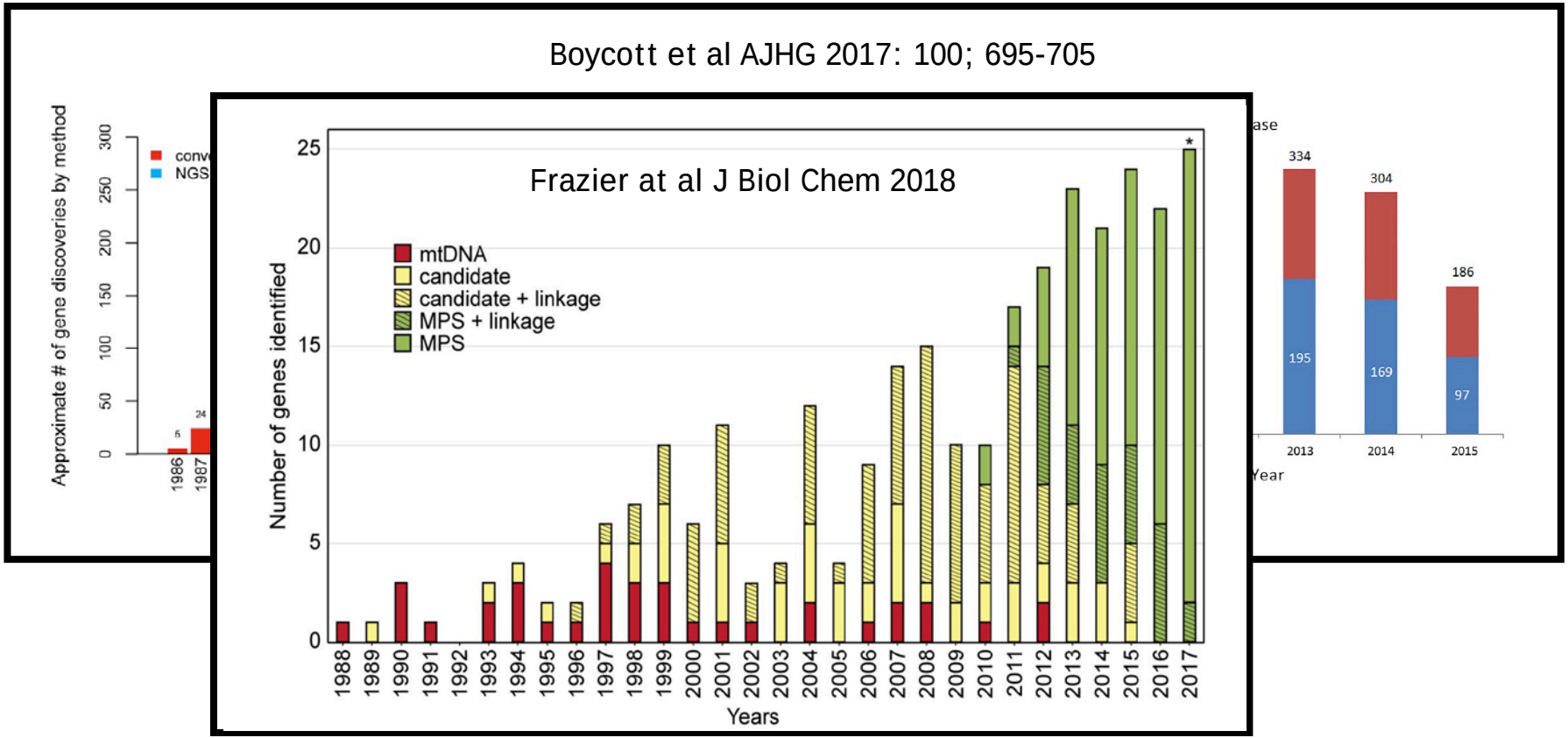
- prolonged, expensive and intrusive diagnostic odyssey



Source: Rare Cancers Australia & https://www.genome.gov/sequencingcostsdata/

Monogenic disorder gene discovery is on the decline……

Boycott et al AJHG 2017: 100; 695-705



…… or perhaps not ……

The promise of genomic medicine in healthcare

Early use of genomic testing provides most benefit

80 infants with ?monogenic conditions 2014-15

Diagnostic yield
Change in management
QALYs gained
Cost per diagnosis

Diagnosis N=48

(19%)

No diagnosis N=32

(3%)

18 months later…

A diagnosis restores reproductive confidence

* Stark *et al* (2016,2017) *Genet. Med.*

Melbourne Genomics Health Alliance

Standard vs Rapid Genomics

	Standard 2014-2015 N=80	Rapid 2016-2017 N=40
Test time	136 days (71-277)	16 days (9-109)
Result during first hospital admission	0	78%
Diagnostic yield	58%	52%
Clinical utility	34%	57%
Cost per diagnosis	$10,788	$13,388
Cost savings	$16,206	$543,178

Early and *FAST* diagnosis matters

5mo hypotonia and seizures

9 months of investigations = $11,928

Clinical diagnosis: Leigh syndrome, fatal

Genomic diagnosis: thiamine transporter defect

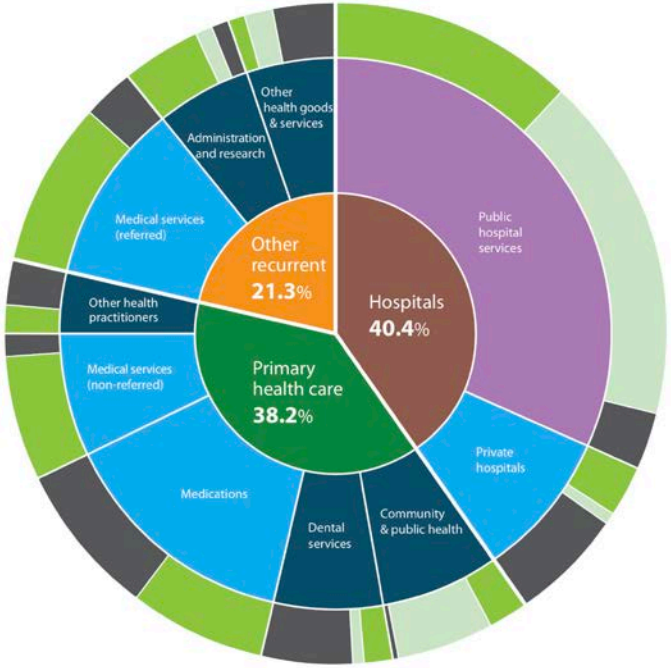
Treatable: thiamine $0.40 per day

No further deterioration

Asymptomatic sister diagnosed, remains well

The Australian Health Care System

COMPLEX AND FRAGMENTED STRUCTURE



Health service funding and responsibilities

Australia's Health 2014, AIHW

Share of expenditure
- Hospitals
- Primary health care
- Other recurrent

Responsibility for services
- Combined private sector and public sector —all levels of government
- State and territory governments
- Private providers

Funding
- Australian Government funding share
- State/territory government funding share
- Private funding share

Australian Genomics Health Alliance

Our Origins: Targeted Call For Research Grant

$25M NATIONAL HEALTH AND MEDICAL RESEARCH COUNCIL GRANT (2016-2020)

Australian Genomics **aims to demonstrate the cost effectiveness, diagnostic efficacy and impact on clinical care of genomic medicine**

~5% of NICU admissions have underlying genetic condition

Need to match the acuity of the clinical situation

Ventilated patient
$4,500 per day

Decisions made over minutes/hours/days

NOT months/years

Genome Medicine

Emergency medical genomes: a breakthrough application of precision medicine

Stephen F. Kingsmore ✉, Josh Petrikin, Laurel K. Willig and Erin Guest

19hrs

Genomic sequencing in acutely ill infants: what will it take to demonstrate clinical value?

Scott D. Grosse PhD ✉ & Lauge Farnaes MD, PhD

Genetics inMedicine

Genome-wide sequencing in acutely ill infants: genomic medicine's critical application?

Jan M. Friedman MD, PhD ✉, Yvonne Bombard PhD, Martina C. Cornel MD, PhD, Conrad V. Fernandez MD, Anne K. Junker MD, Sharon E. Plon MD, PhD, Zornitza Stark BMBCh, DM, Bartha Maria Knoppers PhD & for the Paediatric Task Team of the Global Alliance for Genomics and Health Regulatory and Ethics Work Stream

Australian Genomics Acute Care Flagship – launched in 2018

Approach: Providing **ultra-rapid (<5 day)** genomic testing to acutely unwell infants and children with suspected genetic conditions, with the aim of providing diagnostic certainty and guiding acute care management

Goals:

- Establish clinical and laboratory pathways to deliver ultra-rapid genomic testing

- Comprehensive interdisciplinary evaluation of ultra-rapid genomic testing in acute paediatrics

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Australian Genomics Acute Care Genomics Flagship, N = 70

Diagnostic yield 35/70= 50%

Average TAT 79hrs

(48hrs-167hrs)

50-60% change in management
50% of diagnoses have high recurrence risk

SYND	METABOL	NEURO	OTHER
PTPN11 (3)	*TANGO2*	*ELP2*	*ABCC6*
RIT1	*mtDNA (2)*	*GRIN2A*	*CRYAB*
NF1	*LARS2*	*SCN1A*	*KCNJ1*
SMARCB1	*ECHS1*	*STXBP1*	*SPINK5*
CHD7	*ATP7A*	*GLRB*	*TGM1*
RET	*ALG1*	*RYR1*	*PHOX2B*
GATA3	*PPP1R21*	*COLQ*	
TAF1	*PCCA*	*MYMK*	
SOX11	*HSD17B10*		
HUWE1			

VCGS Leaders in Genetic Health

SEALS excellence in diagnosis research teaching

Australian Genomics Health Alliance

Beyond the exome – the hard(er) stuff!

- phenotypic expansion (~18% of genes) and blended phenotypes (~5-8% of cases)
  - tractable bioinformatics/curation challenge - pushing the limits of expert systems?
  - manual curation and clinical experts needed

- non-coding variants and monogenic disease
  - combined WGS and RNA-seq – variants affecting splicing; variants in regulatory regions (5'UTR, 3'UTR, ncRNA)

- oligogenic inheritance (ciliopathies; autism??; mitochondrial disorders??)
  - mitochondrial respiratory chain disorders as a test model?

- tandem repeats & human disease (mutation rate orders of magnitude > SNV)
  - noncoding TR as direct or indirect transcriptional regulators? Alter DNA or RNA structure? Contributors to missing heritability in polygenic disorders or endophenotypes? What about somatic mutation? Epigenetic overlay??

Conclusions

- NGS is the most disruptive new technology this decade in medical practice
- health economic assessments to date very robust
- great opportunities but many risks
- responsible delivery of genomic medicine will need to be tailored for the local healthcare environment
- early engagement with all stakeholders is critical
- a wonderful time to be working in clinical genetics!

murdoch children's research institute

Thank you

Rapid diagnosis programs: single centre experience

Rady Children's Hospital San Diego

Farnaes *et al* 2018
Trio WGS
N=42
Median TAT 7d
Diagnosis 43%

Texas Children's Hospital®

Meng *et al* 2017
Trio WES
N=62
Mean TAT 13d
Diagnosis 50.8%

Clinical utility 30-60% of those diagnosed

The Royal Children's Hospital Melbourne

Monash Children's Hospital

Stark *et al* 2018
Singleton WES
N=40
Median TAT 16d
Diagnosis 52%

Great Ormond Street Hospital

Boukhibar *et al* 2018
Trio WGS
N=24
Median TAT 7d
Diagnosis 42%

Melbourne Children's
Excellence in clinical care, research and education

Australian Genomics Acute Care Flagship – launched in 2018

Many Questions….

Is consent meaningful?

Clinical service delivery model?

How do we deliver<5d TAT?

Barriers to implementation?

Which patients to test?

Cost effectiveness?

How do results impact decisions?

Is this fair use of resources?

Clinical utility?

Diagnostic utility?

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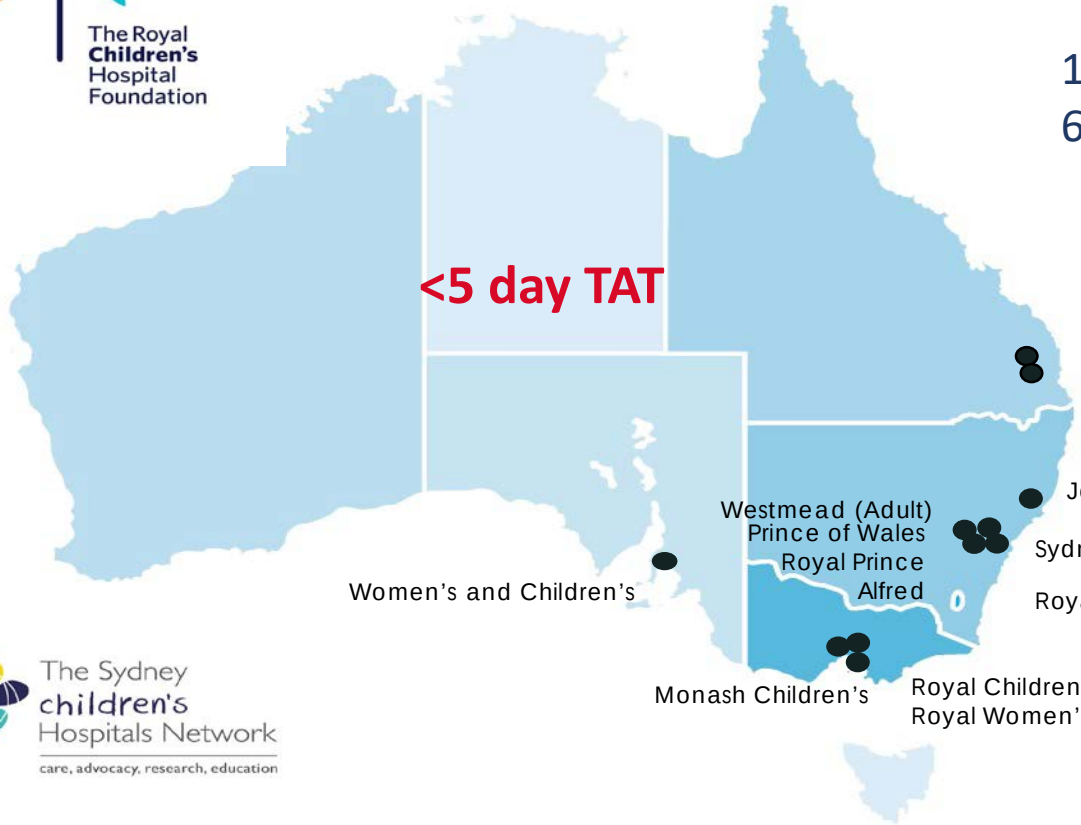
The Royal Children's Hospital Foundation

11 Hospitals
8 Genetic Services

11 NICUs (Level 3)
6 PICUs



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The Sydney children's Hospitals Network
care, advocacy, research, education

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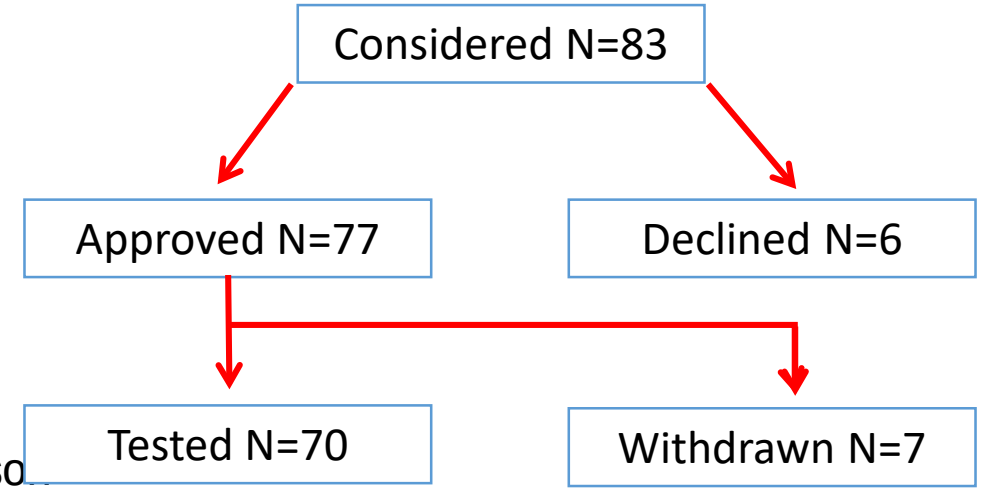
Acute Care Genomics Flagship, N=70

Inclusion criteria
NICU/PICU patient
Likely monogenic disorder
Other inpatients: clinical utility

Exclusion criteria
Secure clinical diagnosis
Non-monogenic cause likely
Imminent discharge/death

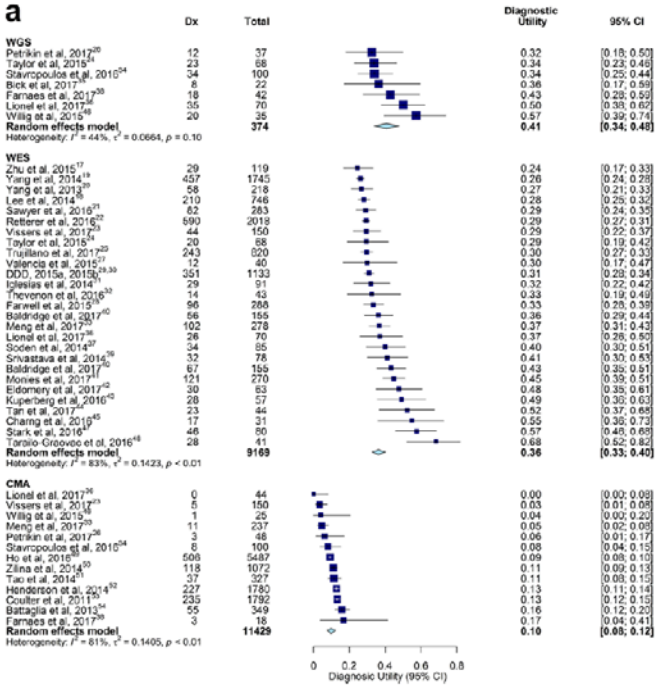
All cases approved by national panel
John Christodoulou, Meredith Wilson, Jason Pinner, Chirag Patel, Zornitza Stark, Chris Barnett

Referral source



Average time to approval 130 min (10-756)

The revolution in rare disease diagnosis



ARTICLE OPEN

Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected genetic diseases

Michelle M. Clark[1], Zornitza Stark[2], Lauge Farnaes[1,3], Tiong Y. Tan[2,4], Susan M. White[2,4], David Dimmock[1] and Stephen F. Kingsmore[1]

37 studies, >20,000 paediatric patients

WES/WGS are x 3-4 more diagnostically effective than chromosomal microarray

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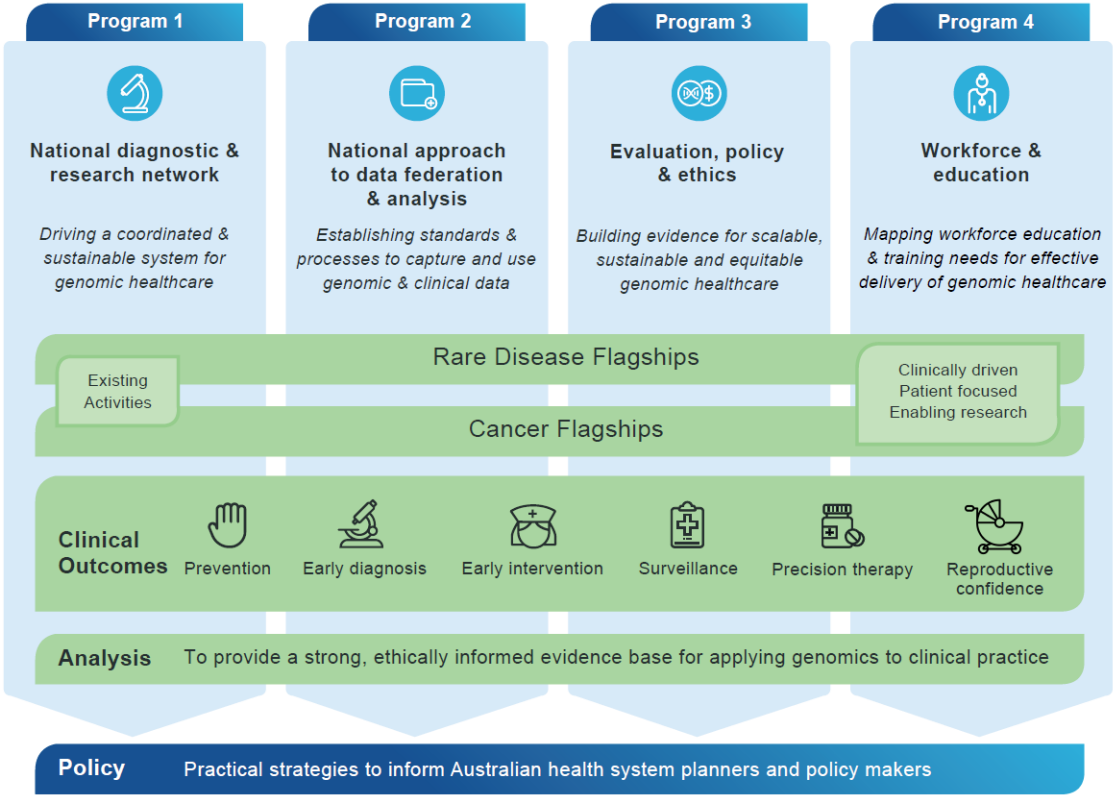
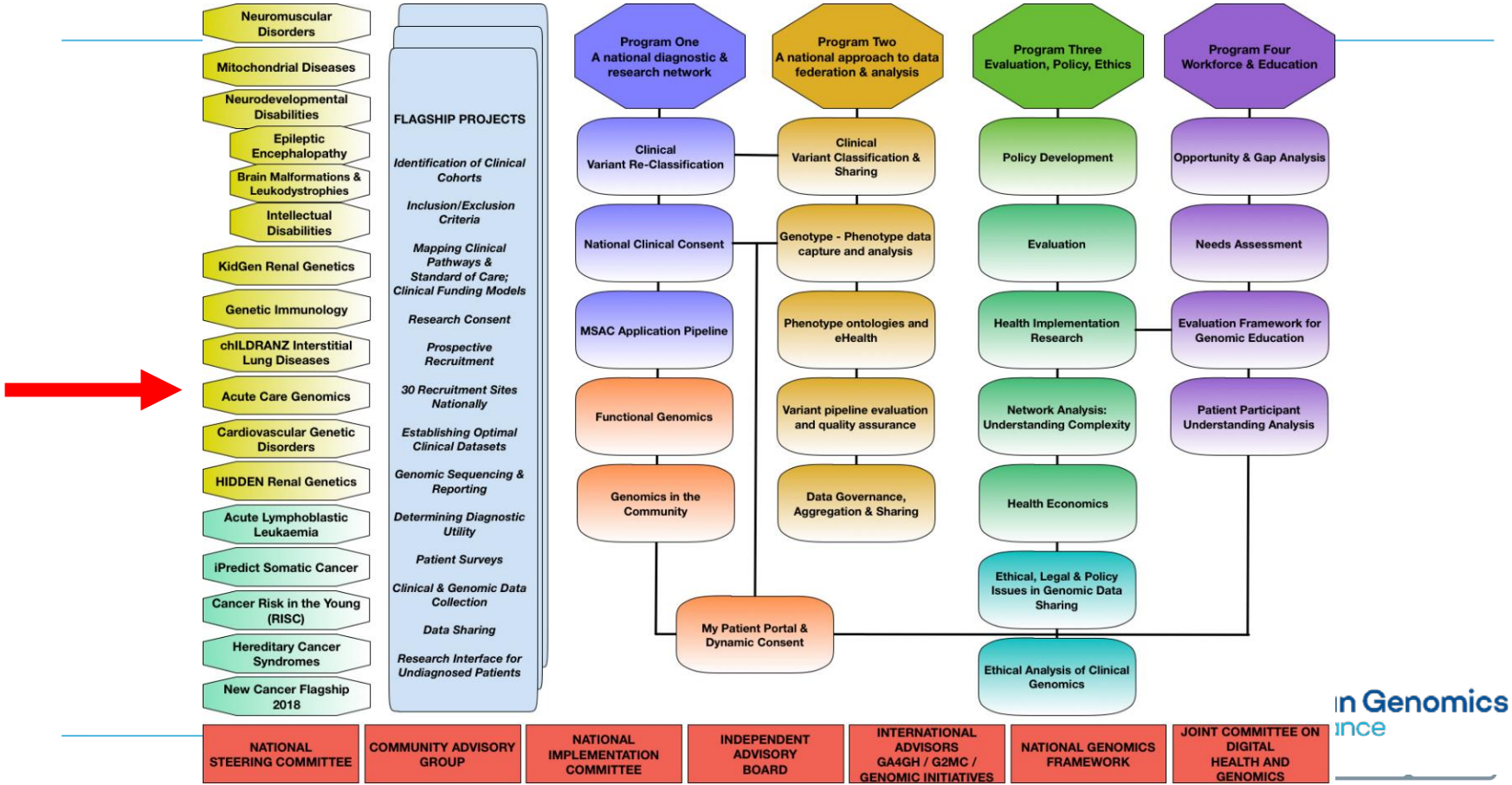
Australian Genomics
NATIONAL HEALTH SERVICES RESEARCH PROGRAM



Australian Genomics Health Alliance

Australian Genomics
PROGRAMS, FLAGSHIPS AND PROJECTS



Acute Care Flagship

Clinical Lead: Zornitza Stark

VIC: **John Christodoulou**, **Emma Krzesinksi**, Matthew Hunter, Sue White, Tiong Tan, Katherine Howell, Lauren Akesson, Andrew Fennell, Chris Richmond, Smitha Kumble, Joy Lee, Heidi Peters, Michelle De Silva, Sam Ayres, Gemma Brett, Ivan Macciocca, Lyndon Gallagher

NSW: **Jason Pinner**, Sarah Sandaradura, Meredith Wilson, Kirsten Boggs

QLD: **Chirag Patel**, Michael Quinn, Jonathan Rogers, Megan Higgins, Lauren Hunt, Lindsay Fowles, Sarju Mehta, Di Milnes, Pathology QLD

SA: **Christopher Barnett**, Sarah King-Smith

Laboratory Lead: Sebastian Lunke

VCGS Pathology: Belinda Chong, Dean Phelan, Miriam Fanjul-Fernandez, Justine Marum, Vanessa Siva Kumar, Jessica Riseley, Steffi Eggers, Simon Sadedin, Chris Ieng, Damien Zammit, Maelle Le Moing, Zeliha Hizli, David Thorburn

Randwick Pathology: Michael Buckley, Tony Roscioli, Edwin Kirk

Australian Genomics:

Tiffany Boughtwood, Keri Pereira, Matilda Haas, Jade Caruana, Tessa Mattiske, Dotti Tang

Evaluation

Workforce/education: Clara Gaff, Belinda McClaren, Amy Nisselle, Fiona Lynch, Melissa Martyn

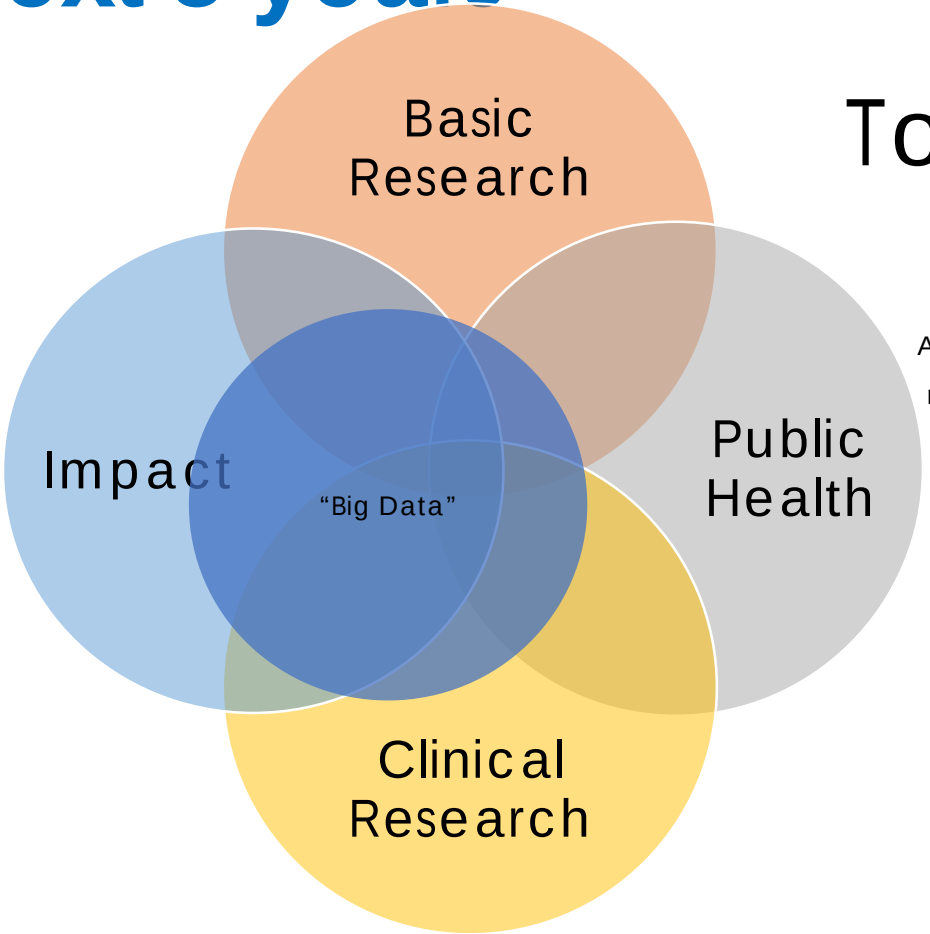
Health economics: Ilias Goranitis

Ethics: Julian Savulescu, Ainsley Newson, Chris Gyngell, Dominic Wilkinson

Implementation science: Stephanie Best, Janet Long, Jeffrey Braithwaite

Family surveys: Melissa Martyn

Next 5 years



Towards Precision Child Health

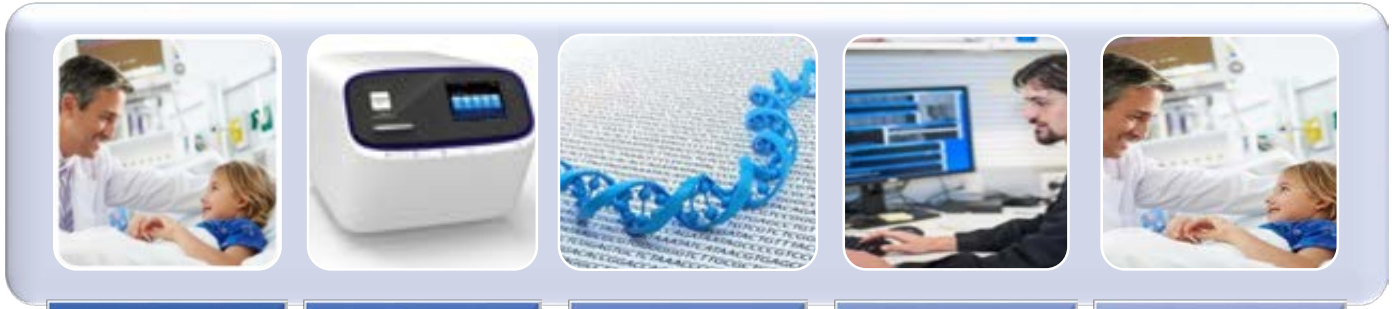
Approach to discover and develop medicines, vaccines or routes of intervention that enable disease prevention and deliver superior therapeutic outcomes for patients,

by integrating ‘big data’ –

clinical, multi-omics, environmental and behavioural information –

to understand the biological basis of disease.

The genomics journey



Pre-test care	Data	Automated analysis	Classification & Reporting	Post-test care
Clinician Tools	Genome data repository	Analysis platform	Curation tool	Clinician Tools
Tools				Tools

From Melbourne Genomics Health Alliance