Missing … presumed well? Ethical and legal aspects of ‘missed cases’ in genomic newborn screening

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This talk is being given on Gadigal lands. The presenters acknowledge these lands were **never ceded**.

We pay our respects to Aboriginal and Torres Strait Islander peoples – including elders past and present.

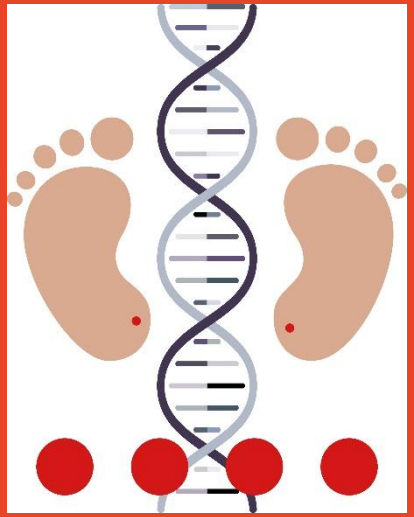
For thousands of years the Gadigal Peoples have shared and exchanged knowledges for the benefit of all.

We stand for a future that profoundly respects and acknowledges Aboriginal perspectives, culture, language and history

Introduction and Setting the Scene

- Introducing the panel
- Our collaboration with Associate Professor Sarah Norris and team, Uni of Sydney ‘gEnomics4newborns: Integrating Ethics and Equity with Effectiveness and Economics for genomic newborn screening’ Medical Research Future Fund, grant MRF2015965
- Our purpose: examining ethical and legal issues of ‘missed cases’ (actual or perceived) in genomic newborn screening through the lens of two case studies

Introduction to ‘missed cases’ in genomic newborn screening



Ainsley Newson

“Missing … presumed well? Ethical and legal aspects of ‘missed cases’ in genomic newborn screening.”
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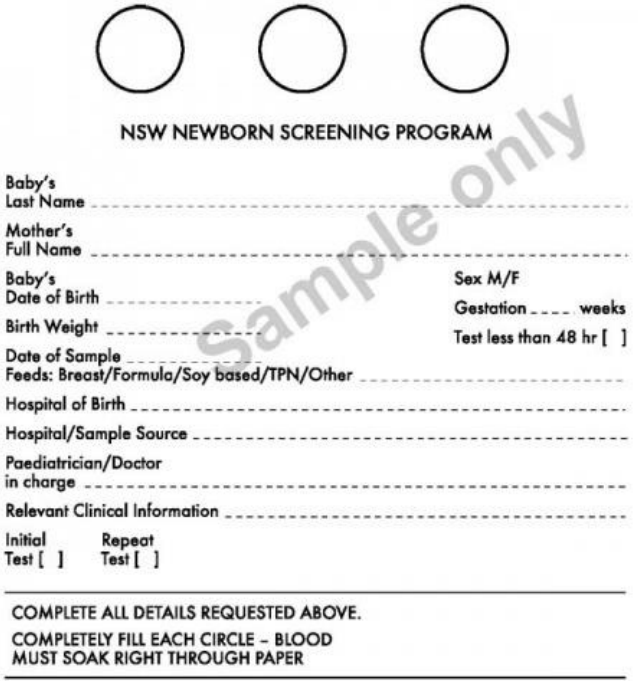
Newborn Screening

Newborn screening

- Formal population health screening program, overseen by a national policy framework
- Established for several decades
- ~99% uptake in Australia (voluntary)
- **Aim**: to identify newborns at risk of serious, rare conditions where early intervention will prevent or mitigate a condition


NSW NEWBORN SCREENING PROGRAM

Sample only

Baby's Last Name

Mother's Full Name

Baby's Date of Birth

Sex M/F

Gestation ____ weeks

Birth Weight

Test less than 48 hr [ ]

Date of Sample

Feeds: Breast/Formula/Soy based/TPN/Other

Hospital of Birth

Hospital/Sample Source

Paediatrician/Doctor in charge

Relevant Clinical Information

Initial Test [ ]

Repeat Test [ ]

COMPLETE ALL DETAILS REQUESTED ABOVE.

COMPLETELY FILL EACH CIRCLE – BLOOD MUST SOAK RIGHT THROUGH PAPER

Newborn screening

- Currently: primarily biochemical
- Changes under consideration
  - Expanding the number of conditions screened
  - Introduction of genomic sequencing as a first line test
- Rationale for changes:
  - ‘Robustness’ of the program
  - ‘Increase early detection’
  - Human right to information
  - ‘Best start in life’

Genomics in newborn screening

Genomics in NBS

- No decision yet on whether to introduce genomics into NBS
- If genomics is introduced, model for its use also not yet known. Options:
    - ‘Second-line’ test
    - Adjunct to current testing (i.e. first line test, but selected conditions)
    - Whole exome
    - Whole genome

Genomics

- Possible to obtain much more data
  - to possibly interpret…
  - … and possibly report

- We are interested in the ethical and legal implications that may flow from this ability to ‘see’ more data

- **One can imagine that stakeholders may have expectations that everything that can be seen should be reported**

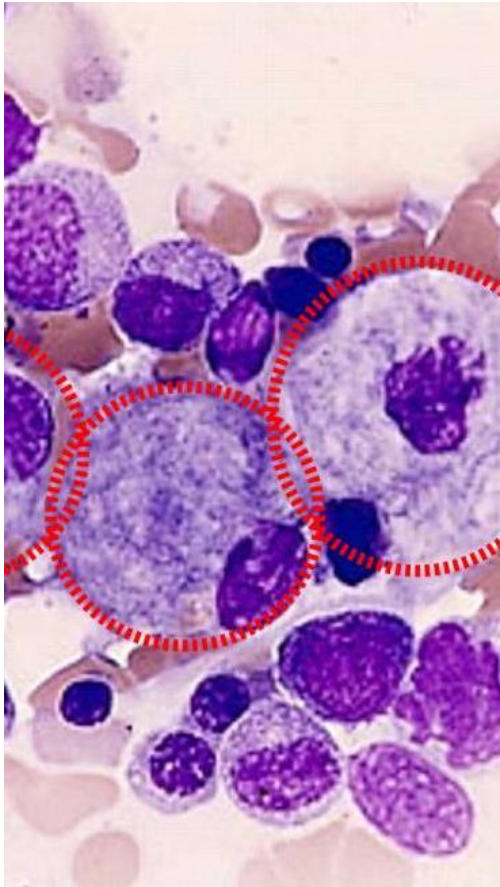
‘Missed cases’?

Detection rates and genomics

- “A 100% chance of a ‘missed case’”
    - It will never be possible to find every single newborn with a dominant or x-linked genetic condition
- Two reasons:
    1. Technology
    2. Variant classification (as pathogenic, likely pathogenic, VUS or benign)

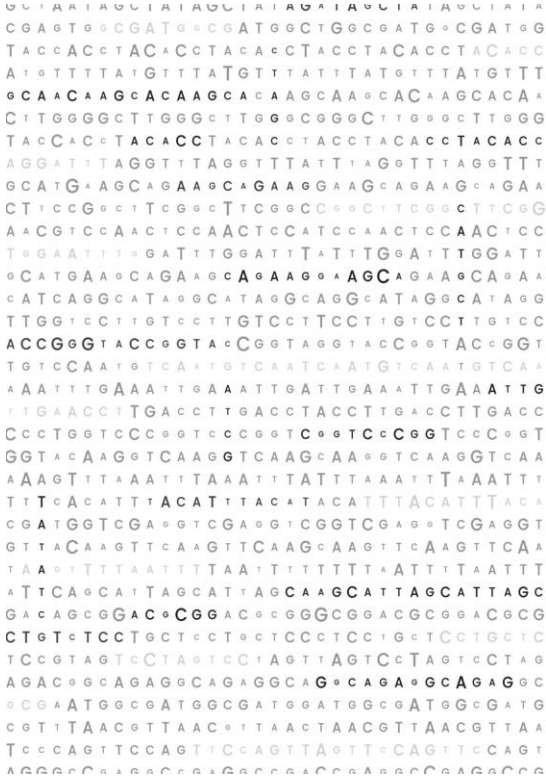
Case study: GBA1 – Gaucher disease

- Leah is born in Illinois, USA. Her NBS results were ‘normal’, but at 6 months, Leah began to show signs of not meeting milestones. She bruised easily and seemed more tired than other babies. Her parents Rebecca and David took Leah to their pediatrician. After initial investigations, subsequent genetic testing showed Leah had Gaucher disease, due to a variant in GBA1. This was not picked up on NBS even though Illinois screens for Gaucher. Her variant was rare and so was not on the screening panel.
- Rebecca and David were concerned that Leah’s Gaucher was not detected, even though she was screened for this condition.



Case study: RYR1

- Priya and Rajesh live in Adelaide. Their first child, Aarav, appeared healthy at birth, and gNBS did not detect anything of concern. gNBS did not screen for variants in the RYR1 gene, associated with malignant hyperthermia and some myopathies.
- At 6 months, Aarav was showing muscle weakness and was missing physical milestones. After waiting for a specialist appointment with a pediatric neurologist, they underwent a battery of tests, and a RYR1 mutation was found.
- Priya and Rajesh questioned why RYR1 was not something looked for routinely in all newborns.



Missed Cases – Ethical considerations

Dr Gabriel Watts

Sydney Health Ethics

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Clinical testing vs Population Screening

Clinical Testing	Population Screening
• Tailored approach to individual context	• Single test offer, same for everyone
• Emphasis on individual/ family outcomes	• Aim to improve outcomes across population
• Individualised care	• Standardised processes, like consent
• Primarily symptomatic patients	• Primarily healthy test subjects

With thanks to Dr Lisa Dive

Clinical testing vs Population Screening

Both clinical testing and population screening *ultimately* aim to diagnose instances of the conditions tested/screened for.

Ethical difficulties arise when reasonable diagnostic expectations in a clinical context depart from reasonable diagnostic expectations in a population health context.

Case Study 1

- Leah is born in Illinois, USA. Her NBS results were ‘normal’, but at 6 months, Leah began to show signs of not meeting milestones. She bruised easily and seemed more tired than other babies. Her parents Rebecca and David took Leah to their pediatrician. After initial investigations, subsequent genetic testing showed Leah had Gaucher disease, due to a variant in GBA1. This was not picked up on NBS even though Illinois screens for Gaucher. Her variant was rare and so was not on the screening panel.
- Rebecca and David were concerned that Leah’s Gaucher was not detected, even though she was screening for this condition.

Case Study 1 - Leah

- Leah's variant was detected by *clinical* genomic testing and she was diagnosed.
- Leah was not missed due to the insensitivity of the test.
- Leah's variant was not screened because it was rare (let's also assume weak evidence (e.g. variable expressivity)).
- Leah was "missed" due to panel design decisions.

Two approaches - #1

1. gNBS as a scaling up of clinical care to population level

- Discrepancies between clinical diagnostic outcomes and diagnostic outcomes after screening are morally problematic and ought to be minimised. Leah was *morally* missed.
- Reporting variants with weaker evidence bases is acceptable when appropriate follow up care is provided.
- The creation of patients-in-waiting is (in principle) acceptable to the end of aligning screening and clinical diagnostic outcomes.
- Rhetorically packaged as ‘precision’ medicine/public health.
- Rationalised as an innovative departure from ‘one size fits all’ medicine towards ‘personalised’ medicine.

Two approaches - #2

2. gNBS as a new 'species' of genomic intervention

- Aiming for clinical diagnostic outcomes when testing a healthy population without clinical triage or family history is a form of hubris. gNBS is a distinct intervention to clinical diagnostic genomic testing with different ethical considerations and demands. Leah may have been harmed by screening, but neither she nor her parents were *wronged*.
- Genomic testing at population level is inherently *im*precise: creating 'patients-in-waiting' to the end of minimising perceived misses masks this fact (even if the harm of doing so is minimal and the benefit of finding fringe cases is significant).
- Substantially increasing false-positive rates threatens overall trust in newborn screening. This jeopardises the interests of newborns who can benefit from population level genomic testing for the sake of marginal increases in diagnostic yield.

Case Study 2

- Priya and Rajesh live in Adelaide. Their first child, Aarav, appeared healthy at birth, and (genomic) newborn screening did not detect anything of concern. gNBS did not screen for variants in the RYR1 gene, associated with malignant hyperthermia and some myopathies.

- At 6 months, Aarav was showing muscle weakness and was missing physical milestones. After waiting for a specialist appointment with a pediatric neurologist, they underwent a battery of tests, and a RYR1 mutation was found.

- Priya and Rajesh questioned why RYR1 was not something looked for routinely in all newborns.

Case Study 2 - Aarav

- Even though gNBS is a different species to clinical diagnostic testing, they are related:
  - gNBS builds on existing clinical practices and infrastructure (e.g. lab services, variant interpretation, genetic counselling).
  - Important to avoid ‘category creep’
    - RYR1 is on the American College of Medical Genetics’ list of Secondary Findings, although ACMG does not recommend it be used in screening
- Even though gNBS is a different species to clinical diagnostic testing, they are in the same ecosystem:
  - Should Aarav’s genome sequence have been stored and made available after screening to potentially reduce his clinical ‘diagnostic odyssey’?

Missed cases

Legal questions

Legal issues generally

- Some are common to any screening program, eg:
  - The process and scope of consent
  - Privacy protections of data
  - Reporting duties: what to report
  - Duty of care
- Some take on new dimensions with gNBS:
  - Who has a right to know or not to know
  - Consent for secondary uses and longevity of consent

Duty of care

- A duty of care is the legal obligation or responsibility to take all reasonable steps to avoid causing foreseeable harm to another person or their property.
- Failing to fulfil that obligation or responsibility can give rise to liability for the harm caused
- Key questions considered in determining whether a breach has occurred:
  - What is the standard of care expected?
  - Did the duty holder fall below that standard of care?

gNBS - Duty of care

- In the case of duty of care, where might harms be caused:
  - At the point of reporting findings
  - At the point of analysing data
  - At the point of conducting the screening
  - At the point of taking the sample
  - At the point of deciding what conditions and what variants will be tested for

The case studies

- Both involve situations where the relevant genetic variant was not screened for
- The cases were both missed because of decisions about what to include in the screening analysis – panel design decisions:
  - Leah: a rare variant to GBA1 not included in the analysis for Gaucher disease
  - Aarav: a variant in RYR1 where no analysis of RYR1 conducted
- Decisions about what conditions to screen for are made by health ministers on the recommendations of the MSAC
  - Likely to be very difficult to establish a failure to meet the relevant standard of care with that decision making given the level of expertise and rigour in the process

Other ‘missed’ case

- False negatives: where the screen analysis misses a ‘positive’ result
- Harm arises due to a failure at a different stage of the process:
  - No longer due to panel exclusion of condition or variants
  - Due to an error in the analytical process
- Liability, if established, would be likely to sit with the testing laboratory

Expectations

- Both Leah's and Aarav's cases demonstrate a level of expectation that the system ought to have identified the relevant variant(s).
- Arguably the introduction of gNBS will raise expectations:
  - Heightened awareness of screening through improved consent procedures
  - Sense of the infallibility of science and particularly genomics
  - Sense that when there is a failure to identify, there should be some remedy for the delays and heightened anxieties
- Impact on trust in the NBS if there is public awareness of expectations not being met (media stories, etc)

Managing expectations

- Information provision needs to be:
  - Timely
  - Designed with the diverse health literacy levels and communication needs of the Australian community
  - Accessible in terms of the health and scientific information being communicated
  - Realistic in what can and cannot be achieved through screening
- Consent needs to be:
  - Timely (not during the immediate aftermath of the birth process)
  - Fully informed by what is and what is not within scope

Thank-you!

The ‘gEnomics4newborns: Integrating Ethics and Equity with Effectiveness and Economics for genomic newborn screening’ project is funded by the Commonwealth of Australia Medical Research Future Fund, grant MRF2015965.

https://genomics4newborns.sydney.edu.au/