Should adult-onset or untreatable conditions be reported in genomic newborn screening programs?

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This talk was prepared on Dharawal land, which I acknowledge was never ceded. I pay my respects to Aboriginal and Torres Strait Islander peoples – including leaders past, present and emerging.

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Why group adult-onset & untreatable conditions together?

- Adult-onset and untreatable conditions are conditions that newborn screening programmes do not conventionally screen for.
- Why not?

Wilson and Jungner, Principles and Practice of Screening for Disease, 1968

"Of all the criteria that a screening test should fulfil, ***the ability to treat the condition adequately, when discovered, is perhaps the most important***. In adhering to the principle of avoiding harm to the patient at all costs (the *primum non nocere* of Hippocrates), treatment must be the first aim [i.e., *not experiment*] … ***when new territory is being explored by the earlier detection of disease***, it is clearly vital ***to determine by experimental surveys*** whether a better prognosis is given by treating the conditions found at an earlier stage than was previously the practice. (p27-8)

- NB: Screening and Research *kept separate*.

Why would adding genomic sequencing into NBS legitimate screening for adult-onset or untreatable conditions?

Watson, et. al., ACMG Newborn Screening Expert Group; ***Newborn Screening: Toward a Uniform Screening Panel and System***. *Genet Med*. 2006 (p.17)

The availability of multiplex testing increases the number of conditions that can be considered for newborn screening that otherwise might not have been considered for screening using traditional criteria, such as incidence and treatability. ***Thus, our perception of screening performance characteristics is also modified***…

Although information about conditions for which treatment options are scarce or not yet reported can lead to increased stresses on families and the health care system, ***early information can also lead to knowledge of the condition for the family***, thus avoiding a potential diagnostic odyssey or inappropriate therapies.

In addition, ***early information provides opportunity for better understanding of disease history and characteristics, and for earlier medical interventions that might be systematically studied*** to determine the risks and benefits.

Multiplex testing and ***the identification of conditions falling outside of the uniform screening panel provides the opportunity for such conditions to be included in research protocols***. Therefore, the criteria used to include a condition in a mandated newborn screening panel are not necessarily straightforward scientific or clinical criteria, but often involve complex ethical, legal, and social policy decisions.

- NB: Screening and Research *merged*.
- Genomic sequencing within NBS amplifies the issue/potential benefits

Why does this matter?

- “Of course it matters, I want to know whatever I can about my child’s future health risks and I want to know as early as possible.”
  - We are not concerned with “pure” ‘value of knowing’ cases here.

- We are interested in cases where “adult-onset” and “untreatable” are contestable (and may be screened for in some places, but not others), and further research is needed to settle the issue.
  - E.g.,: Krabbe, Pompe…

Here the question of the value of using screening for research is pressing.

Why does this matter?

Is a two-tiered consent system an ethically justified solution?

Tarini and Atkins. ***The Krabbe Conundrum Is Really a Newborn Screening Conundrum***. *JAMA Pediatr.* 2023;177(10):1007–1008.

To move NBS forward, we propose the development of a "learning NBS system," akin to the learning health system model. By leveraging a learning NBS system, we will avoid the conundrum of waiting for critical data that never come … ***Within this system, the current limited consent NBS model and a new consented NBS model would coexist***.

The current model would screen for conditions (and add them to the RUSP) for which we can deliver the net direct benefit to all screened and are justified in permitting limited dissent. [Tier 1]

The consented model would serve as a mechanism for collecting critical data (e.g., phenotypic heterogeneity and harms of indeterminate results) to help us decide when screening for a disease is ready for the limited consent model—the learning part of this enhanced NBS system. [Tier 2]

Some may raise concerns that a second-tier consented panel will increase the number of individuals opting out of the current quasi-mandatory panel. ***Given the stakes, this is a testable hypothesis worth testing***—and one that can be mitigated with appropriate education of parents and practitioners."

Why think it is

- There is no other feasible option
  - Tarini and Atkin: “It is infeasible to conduct research studies outside the NBS system to identify the phenotypic variability (including indeterminate cases) and collect critical data on benefits and harms; yet, collecting such data inside the current limited consent system is not ethically or legally sound.”
- *g*NBS is a hybrid intervention – clinical medicine/public health/research
  - gNBS as a “Learning Healthcare System”

Can soliciting clinical/research levels of consent be rendered compatible with the ethical demands of a universal, routinised public health intervention?

It can be, but innovation is necessary

This conundrum is not one we can innovate our way out of…

Why think it is

- gNBS is “precision medicine”
  - Not in a boosterism, catch-all for innovation way.
  - But in a healthcare ideology way, amenable to ideology critique.
- And here is some ideology critique:
  - Juengst et al., ***From "Personalized" to "Precision" Medicine: The Ethical and Social Implications of Rhetorical Reform in Genomic Medicine.*** Hastings Cent Rep. 2016 Sep;46(5):21-33.
  - “In this paper, we report results from interviews with 143 proponents of personalized genomic medicine ***to help explain*** this rhetorical shift and ***the “rebranding” of the movement [to ”precision medicine”]…***
  - “our interviews ***highlight two ideological shifts*** in the emerging practice of genomic medicine that the movement’s rebranding both marks and masks. The first is ***a turn away from “patient empowerment” and toward expert-mediated decision-making in the clinical setting*** reviving debates over medical paternalism that long seemed settled, at least in clinical genetics.

Why think it is

- "Precision medicine" was chosen … to convey its sense that genomics and other emerging biodata sciences ***could improve medicine's clinically defined nosology***. Redefining clinical disease entities ***in terms of specific molecular causal factors could allow clinicians to diagnose more precisely, with presumable benefits for therapy and prevention*** when different molecular diagnoses indicate different responses…
- On the surface, refining disease classifications does not seem like the same thing as stratifying patients into different subpopulations. But they amount to the same thing, to the extent that the science that associates particular molecular markers with different risks, outcomes, and clinical indications is population based to begin with […]
- ***shifting the gaze to classifying diagnoses rather than patients allows "precision medicine" to exploit the popular appeal of "unique tailoring" without giving up the statistical evidence on which measurements rest***.

  - The power shift in *clinical medicine* effected by "precision medicine" is beginning to play out in *public health* under the aegis of gNBS as a "learning healthcare system".
  - Soliciting research/clinical standards of consent at an incredibly vulnerable time is an expression of clinician power and influence over screening programme design, not patient empowerment.

Why be so sure it isn’t?

- Potential exceptions include cases where a strong case for “patient empowerment” through information provision can be made.
  - E.g., Information regarding fatal congenital conditions of infancy that can be used to inform reproductive decision-making.
    - Would need clear co-designed criteria, applied consistently
    - Must guard against scope-creep.

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

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