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The Ethics of Expanded Newborn Screening

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With support from the Claire Giannini Trust

Duane Alexander

- 1974: directed NICHD National Amniocentesis Study.
- 1986-2009: Director, National Institute of Child Health and Human Development
- 1994: Back to Sleep campaign cut SIDS deaths by 50%.
- 2009: Bartholome Award for Ethical Excellence from AAP.
- Now advisor to the Director of the NIH's Fogarty International Center, working on Global Health.

Lainie Friedman Ross

- Carolyn and Matthew Bucksbaum Professor, Associate Director, MacLean Center for Clinical Medical Ethics, The University of Chicago
- Author of:
  - *Children, Families and Health Care Decision Making* (1988)
  - *Children in Medical Research: Access versus Protection* (2006).
  - *The Genetic Testing and Screening of Infants and Children*. (forthcoming)
- Chair: AAP Section on Bioethics
- Ethics committee, UNOS

What tests should be mandated for all newborns?

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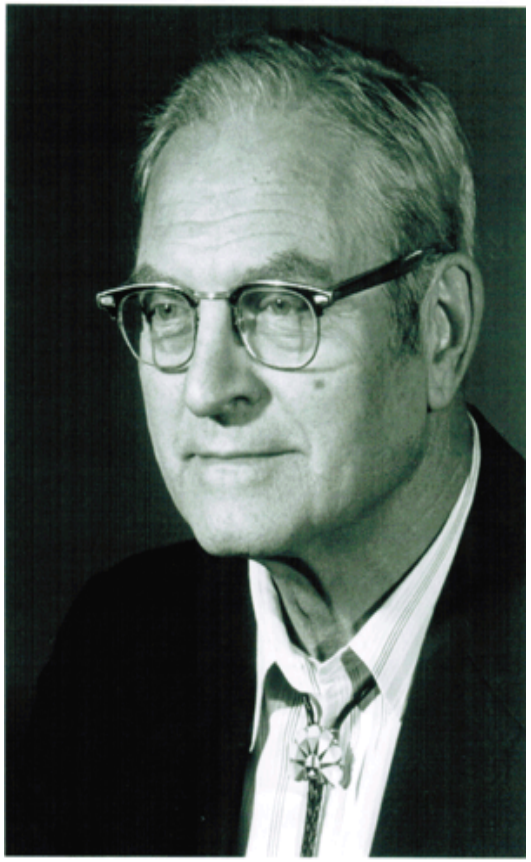
I have nothing to disclose

The History of Newborn Screening



- PKU screening began in the early 1960s after Guthrie developed blood test—Bacterial Inhibition Assay--and card on which to collect blood.
- Controversial at the time
  - Government telling doctors how to practice
  - Not clear that we knew who should be identified as affected and how to treat them or for how long.

Ten criteria for population screening

- World Health Organization (WHO) report by Wilson and Jungner in 1968.
  - Although not specifically designed for newborn screening, it was used, with slight modification, for the next 4 decades.
  - These criteria include an adequate understanding of the natural history of the condition, a recognizable latent or early symptomatic stage, and an agreed policy regarding whom to treat as patients

Box 3.1.1 **Wilson and Jungner classic screening criteria, WHO 1968**

1. The condition sought should be an important health problem
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognisable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a 'once and for all' project.

Wilson . JMG, Jungner G. Principles and practice of screening for disease. Geneva: WHO; 1968. Available from: ***http://www.who.int/bulletin/volumes/86/4/07-050112BP.pdf***

Slightly updated by UK National Screening Committee, "Criteria for appraising the viability, effectiveness and appropriateness of a screening programme". On the web at: http://www.screening.nhs.uk/criteria

Expanding Newborn Screening

- Throughout the 20th century, NBS expanded one condition at a time
- Development of Tandem Mass Spectrometry (MS/MS) allowed for multiplex testing (1990s)
- American College of Medical Genetics (ACMG) / and Human Resources Services Administration (HRSA) considered 83 conditions for consideration in a "Uniform Panel" (2005)
  - Rather than focus on whether the condition met the Wilson and Junger criteria, the ACMG/HRSA committee focused on whether the condition could be screened for using a platform technology
  - Points were awarded for "family benefit" even if no preventive or therapeutic benefit to the child were available

The next technology will be whole genome sequencing.

My position: we need to proceed with caution

My revised position: we need to proceed with more caution than we have employed to-date.

I do NOT object to the technology per se, but the basis for including a condition:

CAN DOES NOT IMPLY OUGHT

Ethical Issues in Expanded NBS

- Lack of Parental Consent for “pilot programs” of unknown sensitivity/specificity
- Identification of variants for which the natural history is not well known
- Identification of variants that do not have onset until adulthood
- Identification of conditions for which treatments do not exist, are experimental, or are not highly efficacious
- Carrier identification and the right to privacy regarding genetic information

Lysosomal Storage Diseases (LSD):
Krabbe
Pompe
Fabry

Case studies from around the world

NBS for Krabbe in the US

- 2005: New York State decides to screen for Krabbe Disorder based on effective parent advocacy
  - Krabbe disease is a degenerative disorder that affects the myelin sheath of the nervous system.
- Krabbe Disease was nominated for inclusion in the uniform newborn screening panel in 2007, and Secretary Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) had a systematic evidence review performed.
  - Based on the evidence, SACHDNC did not recommend inclusion of Krabbe Disease in NBS panels.
- Nevertheless, several states are introducing KD screening (Missouri and IL). Like NY, these states plan to incorporate Krabbe Disease into their mandatory NBS programs, despite the fact that the identification of infantile Krabbe Disease and the timing of hematopoetic stem cell transplant remain experimental.

Krabbe NBS in New York

- Between August 2006-June 2008, 550,000 babies have been screened.
  - 4 high risk
    - 3 were transplanted (<28 days)
      - 1 died
      - 1 severe developmentally delayed
      - 1 doing well
    - 1 did NOT get transplant; died < 1 year
  - 6 moderate risk children
    - None with disease to date
  - 15 low risk
    - None with disease to date
- What we have learned
  - Expected incidence 1/100,000. Expected 5 abnormals; instead 25.
  - Expected 90% of Krabbe would have infantile form; instead 20% and only 8% of infants have manifested early infantile phenotype
- We have learned at the expense of extensive follow-up of these children.
- **No** data to date about parental experiences.

Treatment: Hematopoietic Stem Cell Transplantation

- Escolar's data of 11 asymptomatic newborns and 14 symptomatic infants
  - Asymptomatic
    - 100% engraftment and survival
    - developmental delays developed in all children
  - Symptomatic:
    - 100% engraftment;
    - 43% survival at median follow-up 3.4 years
    - Minimal neurological improvement
- Question about whether the neurological harm may have been exacerbated by the pre-transplant myeloablation, and new protocol uses reduced-intensity myeloablation.

Ethical Issues about NBS for Krabbe

- Krabbe is part of mandatory NBS in New York
  - This is clearly experimental; so children are being enrolled in research without parental consent.
- Even if one argued that this protocol is current "best practice", it is not clear, given the results to-date, that the benefits outweigh the risks. Therefore treatment should NOT be compelled.
  - To-date parents in New York have been allowed to refuse follow-up, even to refuse bone marrow transplant.
- No data are being collected about parental experience with intensive follow-up. We may be causing a great deal of psychosocial harms.
  - We do know that less than half of the parents have returned for all of the neuropscyh testing that the protocol proposes (Duffner et al. *J Peds.* 2012).

NBS for Pompe and Fabry around the world

- NBS for Pompe Disease was developed as a research protocol in Taiwan
  - (Autosomal recessive condition with variable but progressive intralysosomal glycogen storage disease in skeletal, heart and smooth muscles.)
- NBS for Fabry Disease was developed as a research protocol in Italy
  - (X-linked condition caused by the deficiency of the enzyme alpha-galactosidase A (alpha-Gal A). Renal, cardiac and neurologic variants)
  - Although X-linked, women are not necessarily "healthy" carriers but may have full range of symptoms
- Both programs had IRB review and required parental permission
- Both conditions have similar problems to NBS for Krabbe disease
  - Most individuals identified have adult-onset conditions.

NBS for LSD

	Pompe	Fabry	Krabbe
Screening test exists	Yes	For boys; will miss significant # of girls	Yes
Diagnostic test can accurately distinguish infantile from later onset	No (early: late::2:1)	No (early: late::11:1)	No
Natural history of early onset is understood	Yes, and Learning	Yes	Yes
Efficacious treatment	ERT but ineffective in CRIM- (Cross-Reactive Immunological Material negative) patients	ERT	±HSCT
Agreed upon policy on whom to treat as patients	Mostly	Early Rx once symptoms develop	NO
Ready for inclusion in newborn screening programs?	Not yet. Need to reduce # of false positives	Not yet. 1) Need to decide if will screen only boys?; and 2) Not clear it is needed in infancy	NO

Newborn Profiling via
Next Generation Sequencing

nature Vol 452|17 April 2008|doi:10.1038/nature06884

LETTERS

The complete genome of an individual by massively parallel DNA sequencing

Table 3 | SNPs matching HGMD mutations causing disease or other phenotypes

HGMD accession	Chromosome	Coordinate	HUGO symbol	Gene name	Cytogenetic	Phenotype	Zygosity
CM003589	1	97937679	DPYD	Dihydropyrimidine dehydrogenase	1q22	Dihydropyrimidine dehydrogenase deficiency	Heterozygous
CM950484	1	157441978	FY	Duffy blood-group antigen	1q	Duffy blood group antigen, absence	Homozygous*
CM942034	4	619702	PDE6B	Phosphodiesterase 6B, cGMP-specific, rod, beta	4p16.3	Retinitis pigmentosa 40	Heterozygous
CM021718	9	36208221	GNE	UDP-N-acetylglucosamine 2-epimerase	9p	Myopathy, distal, with rimmed vacuoles	Heterozygous
CM980633	10	50348375	ERCC6	Excision repair cross-complementing rodent repair deficiency, complementation group 6 protein (CSB)	10q	Cockayne syndrome	Homozygous†
CM050716	11	76531431	MYO7A	Myosin VIIA	11q13.5	Usher syndrome 1b	Homozygous†
CM950928	12	46812979	PFKM	Phosphofructokinase, muscle	12q13.3	Glycogen storage disease 7	Homozygous*
CM032029	14	20859880	RPGRIP1	Retinitis pigmentosa GTPase regulator interacting protein 1	14q11	Cone–rod dystrophy	Heterozygous
CM984025	19	18047618	IL12RB1	Interleukin-12 receptor, beta 1	19p13.1	Mycobacterial infection	Heterozygous
CM024138	19	41014441	NPHS1	Nephrosis-1, congenital, Finnish type	19q	Congenital nephrotic syndrome, Finnish type	Heterozygous
CM910052	22	49410905	ARSA	Arylsulphatase A	22q	Metachromatic leukodystrophy	Heterozygous

*Coverage at these SNP positions is less than 5. However, both produce benign phenotypes.
†Coverage at these SNP positions is greater than 5. Both would produce severe phenotypes if they were truly homozygous.

Whole Genome Sequencing
Autosomal Recessive Conditions

- Cockayne Syndrome SIGNS/ SYMPTOMS
- Short stature
- Appearance of premature aging.
- Failure to gain weight and grow at the expected rate (failure to thrive),
- Abnormally small head size (microcephaly),
- Impaired development of the nervous system.
- Affected individuals have an extreme sensitivity to sunlight (photosensitivity),
- Other possible signs and symptoms include hearing loss, eye abnormalities, severe tooth decay, bone abnormalities, and changes in the brain that can be seen on brain scans.
- Cockayne syndrome can be divided into subtypes, which are distinguished by the severity and age of onset of symptoms. (All present in childhood).

- Usher syndrome type I is characterized by:
- Congenital, bilateral, profound sensorineural hearing loss,
- Vestibular areflexia,
- Adolescent-onset retinitis pigmentosa.
- Unless fitted with a cochlear implant, individuals do not typically develop speech.
- Retinitis pigmentosa (RP), a progressive, bilateral, symmetric degeneration of rod and cone functions of the retina, develops in adolescence, resulting in progressively constricted visual fields and impaired visual acuity.

Whose Whole Genome?

- **James Dewey Watson** was born in Chicago, Ill., on 4/6/28
- Nobel Prize in Physiology or Medicine 1962
- Lucky for Watson, his whole genome was not known until he was 80 years old!
- What if the information were given to parents earlier?
  - Risk of vulnerable child syndrome
  - Risk of lower parental expectations
  - Risk of termination (if done prenatally)

Watson and Crick, 1950s

October 1962

What are the justifications for the expansion?

D Alexander and PC van Dyck. “A Vision of the Future of Newborn Screening.” *Pediatrics* 2006; 117: S350-S354

Do these arguments hold morally?

JR Botkin, EW Clayton, NC Fost, W Burke, TH Murray, MA Baily, B Wilfond A Berg, and LF Ross. “Newborn Screening Technology: Proceed with Caution.” *Pediatrics*, 2006, 117: 1793-1799.

N Wald. “Neonatal Screening: Old Dogma or Sound Principle.” *Pediatrics* 2007; 119: 406-407

4 arguments to expand NBS

- Reduce diagnostic odyssey
  - First, we need to improve our diagnostic skills of clinicians
  - Second, such screening will create new diagnostic odysseys, and the voices of these families have not yet been heard.
- Identify family risks for future reproductive planning
  - No need to make children canaries in the coal mine. Bell et al. in 2011 "**Carrier Testing for Severe Childhood Recessive Diseases by Next-Generation Sequencing" identified: "**developed a preconception carrier screen for 448 severe recessive childhood disease"
  - Not everyone wants to know their reproductive risks (need for consent)
- Adjunctive therapy may be useful
  - This would need to be proven for each condition. The Krabbe disease story shows it may also be harmful.
  - It could also lead to unnecessary medical interventions (when conditions will not present for years or decades, if ever), and their attendant risk of adverse effects.
  - To the extent that it would lead to experimental therapies, we require consent.
- Screened infants could participate in research on innovative therapies
  - Yes, but we usually locate research subjects ONLY with consent.

Concluding remarks

- **Mandatory screening** must be restricted to conditions for which early identification can reduce infant morbidity or mortality (modified Wilson and Jungner).
  - BENEFIT to child; family benefits can only be secondary.
- Population-based newborn screening should be piloted before extended to the entire cohort of newborns. This is research and should be done under an IRB approved protocol with parental permission.
- Expanding beyond the Wilson and Jungner criteria should be done with parental permission.
- We need to be humble:
  - there is much we (health care professionals) do not understand
    - (and even more that policy makers do not understand)
  - Genotype ≠ phenotype
  - We need to consider the unintended consequences
- Can does not imply ought!

Questions?

Please type your questions in the Q & A Panel.

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On Thursday, Nov 29th, 12-1 PM CST

Slow Codes, Show Codes and No-Codes

Annie Janvier, MD, PhD
William Meadow, MD, PhD

Email cmbc@cmh.edu for registration information.

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