

Ethical and Policy Issues in Genetic Screening: Case Examples from Newborn Screening

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Objectives

- 1) Discuss the policy and ethical implications of using large scale applications of high throughput technologies in healthy individuals.
- 2) Discuss the policy and ethical implications of large-scale screening of children for conditions with diverse phenotype over the life-span

Case Studies

- 1) Expanding Newborn screening
 - Tandem Mass Spectrometry (MS/MS)
 - Identification of “normal variants”
- 2) Newborn screening for conditions that have early and late-onset presentations
 - Alpha-1 Anti-Trypsin Deficiency (AIATD)
 - Krabbe Disease (KD)

Expanding Newborn Screening

- 1) Tandem Mass Spectrometry (MS/MS)
- 2) Identification of “normal variants”

Expanding Newborn Screening Panels

- American College of Medical Genetics (ACMG) was funded by Human Research Services Association (HRSA) to develop a “uniform panel”.
 - 29 primary conditions
 - 25 secondary conditions (would be picked up by the same technology as the primary conditions; but do not meet screening criteria)
- The ACMG/HRSA report has been criticized for putting too much emphasis on conditions that can be identified by using a platform technology; and not enough emphasis on whether the condition has a safe and effective treatment.

Uniform Panel

- Virtually all of the conditions can be identified by Tandem Mass Spectrometry (MS/MS)
- At one end of the spectrum, PKU and MCAD.
 - And yet as we identify MCAD by NBS, we realize that there is a large number of individuals who are asymptomatic and may never develop symptoms.
- At the other end, 2-methylbutyryl-CoA Dehydrogenase Deficiency (2-MBAD)
 - Before MS/MS only 5 cases identified
 - In first 5.75 years, Wisconsin identified 27 infants, all but one were infants born to Hmong families.
 - Virtually all are asymptomatic despite relative non-compliance with diet.

Variability across the spectrum

- The variability found in MCAD is commonly found when we move from testing individuals with particular symptoms to population screening.
- The finding that some variations are benign is also not novel.
 - Pre MS/MS: Histidinemia
 - MS/MS: 3-methylcrotonyl-CoA carboxylase (3-MCC)
 - Some well-known examples of benign variants currently detected by NBS are benign hyperphenylalaninemia and Duarte galactosemia.

Newborn screening for conditions that have early and late-onset presentations

- 1) Alpha-1 Anti-Trypsin Deficiency (A1ATD)
- 2) Krabbe Disease (KD)

Alpha-1 Antitrypsin Deficiency (A1ATD)

- The homozygous PiZZ genotype (1/5000 in US Caucasian population; wider variation in Europe with incidence up to 1/500.)
 - The [A1AT] in PiZZ individuals is about 15% of normal.
 - The PiZZ genotype accounts for all a1ATD-related childhood cases of liver disease and the vast majority of chronic obstructive pulmonary disease (COPD) cases due to a1ATD
 - 20% of cases of neonatal cholestasis
 - 2–5% of cases of destructive lung disease in early adulthood.
 - This risk is increased with TOBACCO.
- Intermediate A1ATD, caused by the more common PiSZ phenotype
 - The [A1AT] is about 35% of normal
 - Rarely causes health problems

Pilot NBS for A1ATD for adult-onset lung disease

- Newborn screening program began in the 1970s in Sweden and continued for several years.
- Initial program was done as part of mandatory screening.
- While there was some adverse psychological reactions, a review 25 years later found that the screened children understood the significance of A1ATD and were less likely to smoke.
- In 1996, World Health Organization (WHO) recommended newborn A1ATD screening in all developed countries with Caucasian populations.
 - Recommended it be done with informed consent!
- An alternative, “if the potential possibility to prevent liver disease is regarded as mainly hypothetical, screening may be recommended at 11–12 y of age”.

NBS for liver disease?

- Volpert D, Molleston JP, and Perlmutter DH. Alpha1-antitrypsin deficiency-associated liver disease progresses slowly in some children. Journal of Pediatric Gastroenterology & Nutrition. 2000 31(3):258-63.
 - A prospective nationwide screening study initiated more than 20 years ago in Sweden has shown that clinically significant liver disease develops in only 10% to 15% of AIATD children.
 - This study provides information about 85% to 90% of those children, many of whom had elevated serum transaminases in infancy but have no evidence of liver injury by age 18 years. The authors commented on the relatively slow progression and stable course of the liver disease in some of these children.

When Genotype $\neq$ Phenotype

- Hinds R et al. “Variable degree of liver involvement in siblings with PiZZ alpha-1-antitrypsin deficiency-related liver disease.” *J of Pediatric Gastroenterology & Nutrition* 2006; 43(1):136-8.
 - Study identified 29 families with more than 1 child with the PiZZ phenotype.
 - Twenty-one (72%) PiZZ siblings of the 29 probands had liver disease, which was concordant for severity in 6 (29%), while 8 (28%) had no liver involvement.
 - Five of 7 children requiring liver transplantation had siblings with no persistent liver dysfunction.
 - This study suggests that there is a variable degree of liver involvement in siblings with PiZZ.
 - A1ATD-related liver disease and environmental and/or other genetic factors must be involved in determining disease severity.

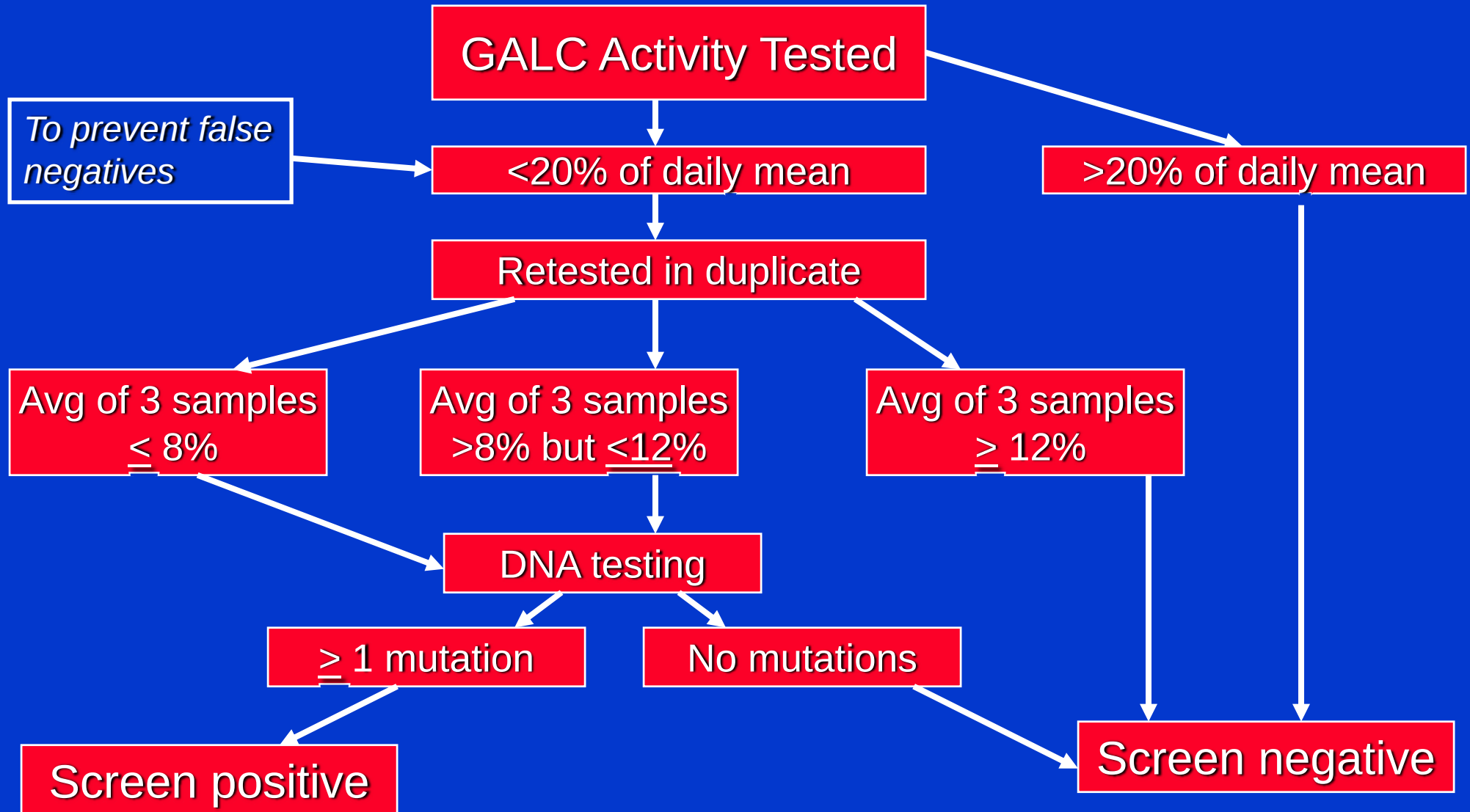
A1ATD Ethical and Policy Issues

- If one ignores the possible benefit of identifying liver disease by A1ATD screening and promotes screening to prevent COPD, the question is the proper timing for such screening?
- If one does not want to ignore the possible benefit of identifying liver disease early, the question is whether A1ATD screening is the proper test or whether bilirubin screening may be more effective?
 - it will pick up biliary atresia
 - It will avoid those with A1ATD that do not present in infancy.

Krabbe Consortium of New York State

- Standardized clinical evaluation protocol
- Criteria for transplantation for the early infantile phenotype were formulated
- Clinical database and registry developed
 - Actually developed by Hunter's Hope Foundation in 1997 and by 2006 had questionnaires from 332 parents of children with Krabbe disease
 - Most represented early-onset
 - (70% < 6 months; 19% between 7mo-1 year)
 - Most common early symptoms were crying and irritability, stiffness, seizures, poor head control, poor feeding and fisting.
 - As disease progressed, crying and irritability lessened as did the spasticity, but was superseded by immobility, loss of vision, loss of smiling, need for NG feeds

Newborn Screening Algorithm



Krabbe Newborn Screening

- Who should be treated?
 - 30-kb deletion
 - Otherwise, genotype $\neq$ phenotype
 - But you need to diagnose presymptotically or you can speed up deterioration.
 - Algorithm for staging (Escolar et al. Peds 2006)

Evaluation Schedule

Schedule	Neuro Exam	Neuro-diagnostic Studies*	Neuro-psych testing
High risk (GALC $\leq$ 0.15 nmol/h/mg protein)			
Baseline	Yes	Yes	No
Year 1	Monthly	If abn neuro/developmental findings; otherwise q 3 months	Annual
Year 2	Every 3 months	If abn neuro/developmental findings; otherwise q 3 months	Annual
Moderate risk (GALC 0.16-0.29 nmol/h/mg protein)			
Baseline	Yes	If abn neuro/developmental findings	No
Year 1	Every 3 months	If abn neuro/developmental findings; otherwise annual	Annual
Year 2	Every 3 months	If abn neuro/developmental findings; otherwise annual	Annual
Low Risk (GALC >0.3 to 0.5 nmol/h/mg protein)			
Baseline	Yes	If abn neuro/developmental findings	No
Year 1	Every 6 months	ONLY If abn neuro/developmental findings	If abn neuro/developmental findings; otherwise annual
Year 2	Every 6 months	ONLY If abn neuro/developmental findings	If abn neuro/developmental findings; otherwise annual

NBS in New York in first year

- Between August 2006-June 2008, 550,000 babies were screened.
 - 4 high risk
 - 2 with mutations and abn neurodiagnostic results received BMT
 - 1 died
 - 1 developmentally delayed
 - 2 did NOT get transplant and are neurologically normal
 - 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. Some protocols are now using reduced-intensity myeloablation.

Ethical Issues

- Krabbe is part of mandatory newborn screening in New York
 - This is clearly experimental; so children are being enrolled in research without parental consent.
 - It is not clear how NY State would respond if parents refused the intensive follow-up regimen, so it is not clear that children can withdraw from the research.
- 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 it is not clear treatment can be (ought to be) compelled.
- No data are being collected about parental experience with intensive follow-up. We may be causing a great deal of psychosocial harms.
- Clearly Krabbe does not belong in the Uniform Panel
- Clearly New York State should obtain parental consent
- Illinois is preparing to introduce Krabbe as part of newborn screening in 2011.

Ethical and Policy Issues in Genetic Screening

- 1) Expanding NBS to include ALL that we can changes NBS from a “public health emergency” to a “public health service”.
- 2) Including conditions that present at different times in the life-span raises the question of whether to include as part of NBS or to screen at another time.
- Both issues push us towards the need for informed consent in NBS.