

Carrier Detection in Newborns: Should it be Discovered? Should it be Disclosed?

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Newborn Genetic Screening:

For Whose Benefit ?

Three Case Studies

- Sickle cell anemia (SCA)
- Cystic Fibrosis (CF)
- Duchenne Muscular Dystrophy (DMD)

Sickle Cell Anemia

- Autosomal recessive disease characterized by anemia and vaso-occlusive events.
- Single point mutation (valine is substituted for glutamic acid in the sixth amino acid of the β -chain)
 - Wide variability in symptomatology.
- ~10% of Black Americans are carriers; about 0.3% have sickle cell anemia.
 - Also seen in other communities (e.g., Mediterranean families).
- Carrier status: Protective against malaria; may have slight increased risk of sudden death, but does not interfere with daily function.

Sickle Cell Anemia Screening-1

- 1972: National Sickle Cell Anemia and Control Act
- 1972: Greenberg et al. described solubility testing (sickledex). Does not distinguish carriers from homozygotes.
- 1973: Garrick et al. described electrophoresis methodology (which could distinguish trait from disease).
 - 1989: Schedlbauer and Pass described electrophoresis on infant blood spots.
- 1987: McCabe et al. demonstrated that DNA can be extracted from dried blood spots on filter paper.

Sickle Cell Anemia Screening-2

- 1970s: Screening focus was Population Screening and screening pregnant women and their partners.
- 1986: Gaston et al. show that PCN prophylaxis decreases morbidity and mortality in infants with SCA.
- 1987: CDC workshop recommends newborn screening for SCA.
 - In 1985, 7 states already testing for hemoglobinopathies along with PKU in newborns.
- By 1990, 29 states offered some type of newborn screening.
 - Often targeted, and not universal.
- 2004: 48 states plus District of Columbia provide universal newborn screening.
 - 2 states screen only selected populations (S.D. and N.H.)
 - 1 state (Idaho) does not offer.

Disclosure of Newborn Carrier Results

- Controversial in the 1970s and 1980s with some states disclosing (New York, Connecticut) and others not (California).
- President's Commission, 1983: Newborn screening should not be done primarily to determine parental carrier results. However, if carriers are identified, parents have a right to know.
- Reaffirmed in IOM Report, *Assessing Genetic Risks*, 1994.
- Today, virtually all disclose carrier results.

PROS and CONS of Carrier Disclosure

● Advantages

- Parents are the appropriate fiduciaries of their child's health information
- Reproductive decision-making of parents
- Relevance for child's reproductive decision making when he or she becomes of age.

● Disadvantages

- Fears of parent-infant bonding issues (unfounded)
- Fears of discrimination (occurred in the 1970s and 1980s)
- Fears of "sickle cell" non-disease
- Takes away child's right not to know

Cystic Fibrosis

- Autosomal recessive disease characterized by gastrointestinal (pancreatic insufficiency and malnutrition) and pulmonary (chronic cough, airway obstruction) manifestations.
- Over 1000 mutations have been identified; and course of illness varies greatly.
 - Genotype-phenotype correlation for gastrointestinal symptoms is okay.
 - Lack of genotype-phenotype correlation for pulmonary symptoms.
- ~4% of Caucasians are carriers; less common in other ethnic communities. .04% Caucasians have CF.
- Carriers are asymptomatic.

Cystic Fibrosis Newborn Screening-1

- 1979: Crossley et al. developed Immunoreactive Trypsinogen (IRT) assay on dried blood spot.
 - CDC workshop 1983: Did not recommend neonatal screening yet. Need for data.
- 1983: Wisconsin begins randomized controlled trial using IRT method.
- 1989: Collins et al discover Cystic Fibrosis gene.
- 1990: Wisconsin changes to IRT/DNA method.
- 1990s: Population and antenatal screening programs begin (low uptake)
- 1997: Wisconsin shows nutritional benefit to newborn screening.
- 1997: CDC workshop: CF carrier screening of pregnant women is ready for prime-time; still need more data to recommend newborn screening.

PROS and CONS of carrier detection

- Allows for a single test with fewer false positives.
- Information is known: information belongs to the family.
 - Even if one believes the information belongs SOLELY to the child, question remains who is the best caretaker of this knowledge.
 - However, a small percentage of parents are confused despite genetic counseling and believe that children remain “at risk”.
- May inform parents of their own reproductive risk.
 - Carrier screening preconception and antenatally has been recommended since 2001. Therefore, adults can have themselves tested and we do not need to use child to inform parents of their risk.
 - Unlike SCA, not all adults who undergo antenatal CF screening and are heterozygous for CF will be discovered; newborn screening provides a safety net for those families.

Cystic Fibrosis Newborn Screening -2

- 2001: American College of Obstetrics and Gynecology [ACOG] recommends universal carrier screening of women antenatally or preconception.
- 2000-2003: More data
 - Wisconsin publishes more data about nutritional benefits (2001)
 - Pulmonary data less clear-cut.
 - Possible cognitive benefits in a subset of CF patients.
- 2003: CDC conference states CF newborn screening is justified.
- Currently, 6 states screen for CF as part of universal screening; mandated in 7th state but not implemented to-date
 - Another 4 states offer as part of pilot or experimental program.
 - All use IRT/DNA methodology and therefore diagnosis carriers.

CF Carriers Diagnosed by Newborn Screening

- NOT all children are tested for CF genes (only those who present with meconium ileus or an elevated IRT).
 - Only expect to diagnosis one in 200 carriers (rather than one-in-25 in the general population).
- Because of the large number of mutations, some children who are classified as NOT “at risk” for CF using IRT/DNA may actually have CF or be a carrier.
 - IRT/DNA is more accurate in Caucasian populations; less accurate in other populations (esp. Asians).
- Testing could be done without DNA
 - Requires a second blood sample.
 - Increased number of false positives.

Duchenne Muscular Dystrophy

- X-linked recessive condition of complete penetrance.
- ~1/3,500 male births
- Infant males are asymptomatic. Onset of neuromuscular degeneration begins in early childhood; requiring a wheel-chair by adolescence and death in early adulthood.
- Female carriers may have some mild skeletal weakness.
 - >10% have some cardiac abnormalities as adults.
- Mothers of two-thirds of affected children are carriers.
 - One-third de novo mutations.

DMD Newborn Screening

- 1959: Ebashi et al. found grossly raised level of creatinine phosphokinase (CPK) in patients with DMD.
- 1962: Hughes and Rosalki developed methods to measure CPK reliably.
- 1975: Zellweger and Antonik: measured CPK off of the Guthrie card.
- 1976: Beckman and Scheuerbrandt introduced newborn screening program for DMD in Germany.
 - Detected 5 boys with preclinical muscular dystrophy which would give an incidence of 1 in 1700 male births.
- Flurry of programs in late 1980s when gene therapy thought to be “around the corner”
 - Most only screen boys, although carrier girls would have elevated CPKs.
 - CPK in carrier girls tend to become normal by adulthood.

PROS and CONS of carrier detection

- Most programs only test boys. Carrier girls can be detected.
- Should we screen girls and boys in order to detect those affected and those who are carriers?
- YES: Justice argument: ensures that carrier girls (who may be symptomatic, although milder and of later onset) are also diagnosed.
- YES: May inform parents of their own reproductive risk.
 - Remember, one third of cases are de novo mutations.
- NO: Since girls are rarely affected, screening girls is solely for the purpose of detecting parental risk. We can test the women themselves.

Carrier Detection in Newborns: Discovery and Disclosure

A Comparative Analysis of the 3 case studies

Newborn Screening in Context

	Population screening	Antenatal screening	Newborn Screening
SCA	1 st	2 nd	3 rd
CF	2 nd	3 rd	1 st
DMD	--	(cascade only)	1 st

- The interrelationship of newborn screening and antenatal screening with respect to carrier detection.
 - Is disclosure of carrier newborns useful or justified when antenatal screening exists?
 - YES: not all women have access to antenatal testing
 - YES: antenatal screening often misses fathers
 - NO: denies a right not to know

Newborn Screening Methodology: Is Carrier Detection Necessary?

SCA	Hemoglobin electrophoresis is a non-genetic test; the results are genetic and uncovers all children who are carriers.
CF	The IRT is non-genetic and gives out no information on carrier status. IRT/IRT requires 2 blood tests and has more false positives than the IRT/DNA. IRT/DNA uncovers carrier status; however, not all children who are carriers are uncovered.
DMD	CPK is non-genetic. If girls are tested, it will uncover most carrier females. CPK in girls becomes normal in adulthood.

Should the Carrier status of newborns be disclosed?

- Yes; this is information that belongs to family.
 - Even if one believes it is information that belongs solely to the child; parents are the best repository until the child comes of age.
- Yes BUT
 - Carrier detection should not be the sole reason for newborn screening.
 - Newborn screening methodologies that can avoid carrier determinations should be considered.
 - In CF, IRT/DNA vs IRT/IRT versus other possibilities.
 - In DMD, testing of only boys avoids the detection of carrier females.

Should the Carrier status of newborns be disclosed?

- Yes BUT:
 - Although data refute impact on parent-child bonding, some parents remain confused. One should not assume that carrier disclosure is benign to all families.
- Yes BUT:
 - Some parents may not want this information.
 - Informed consent prior to newborn screening would allow for non-disclosure, and it would be more respectful of parental autonomy.