Duchenne Newborn Screening in the U.S.

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• Assess how an advocacy groups can be meaningfully involved
  – ensure that patient perspectives are integrated into the consideration process
  – assure the integrity of scientific research and evidence review processes.
• Examine the concept of benefit to include benefit to the family and consider a diagnostic odyssey often experienced by families before a diagnosis is obtained.
  – Benefit needs to consider concept of treatments beyond medical therapies.
DMD ELSI Workgroup

• Evaluate universal versus targeting screening based on gender for X-linked conditions

  – Assess parental permission process when phenotypic variability is unknown

  – Need to consider whether, how and when to report carrier status
Newborn Screening for Duchenne: Should we screen for males or both males and females?
Genetics of Duchenne Carriers

• DMD inherited in an x-linked pattern
  – Inherit the mutation on the X chromosome from the mother: 2/3
  – Other mechanisms include de novo mutation or Mutation in mother’s egg cell/or father’s germ line (or Germ-line mosaicism)

• All females inherit two copies of the X chromosome – one from each parent.
  – Each body cell needs only one functional X chromosome. This is randomly determined, so that all females have a mixture of cells in which the active X is either the maternal or the paternal
Genetics of Duchenne Carriers

• All carriers of DMD have some muscle fibers [multinucleate cells] in which the active X carries the defect
  – problems arising from the fibers with the genetic defect will obviously depend on the proportion of such fibers and their distribution.

• Theory that a compensatory mechanism causes the ‘normal’ cells to produce enough dystrophin to make up the deficiency – this has yet to be demonstrated.
Genetics of Duchenne Carriers

• At least 10% of carriers may have problems
  – BUT, most problems developed later in life, NOT as a child
  – In very rare cases, when the active X carrying the DMD gene is in the vast majority of muscles cells, the female carrier will have DMD as severely as affected males.
  – At the other end of the scale the carrier is most likely unaffected

• Additionally, evidence that the heart muscle can be affected in isolation which again may not become apparent until later in life.
Therefore, **VERY RARELY** female carriers can have similar muscular weakness as affected males and for this reason are termed Manifesting Carriers.

This condition can occur with no known family history of DMD so all females who are suspected of having any form of muscular dystrophy should be tested.

- BUT, remember diagnosed late
- No easy screening test for Manifesting Carriers
  - CK cut off would have to be very low
Need to examine the whole NBS system when looking at ELSI issues and designing pilots
Proposed Distribution of Results: Screening Algorithm for DMD

- CK Testing
  - NBS State Lab
  - CK performed at NBS State Health Lab
  - Normal results sent to Family via Pediatric care provider.
  - Abnormal CK to Emory DNA Laboratory
    - If DMD/BMD mutation found results to Family via MH and referred to DMD Clinic.
    - If female, parents see genetic counselor at DMD Clinic.
    - If other muscular dystrophy mutation found, family informed and sent to DMD Clinic.
    - If CK Elevated and no mutation found, the family is informed and patient advised to follow up in DMD Clinic for re-testing of CK.
DMD NBS Proposed Algorithm

- In the US, usual approach is to screen universally
- Some states report out carriers for some disorders/others do not
- We propose two places for reporting results
- The screen/diagnostic test determines which cases are detected

NORMAL CK

ABNORMAL CK

EMORY DNA LAB

DNA results

Results to Family via MH

DMD Clinic

EMORY DNA LAB
Screening Female Infants: Ethical Issues

Screen Males/Females

- Female carriers may exhibit disease either in childhood or as adults [cardiomyopathy]
- An elevated CK in female infants may be indicative of other forms of muscular dystrophy
  - And Prolonged diagnostic odyssey could have been avoided
- Exclusion of females may be a burden on HC/PH NBS system
- Inclusion of females in NBS program increases general understanding [HC providers/families] of DMD
Screening Female Infants: Ethical Issues

Screen Males only

- CK screen generally does not discern female carriers
  - May be false negatives (huge number if CK level low) and therefore, *false reassurance*
- Early onset of functionally important weakness in carriers is rare
- HC delivery system inadequate to provide QUALITY genetic counseling and testing
  - Inclusion may burden an inadequate system of genetic services
- Offering no clear benefit to majority of female infants
Pilot

• Will need to determine:
  – males only vs universal screening
    • If males only, a deviation that needs to be explained
    • If both, substantial educational/training needs
  – Educational needs for parents/HC providers to understand limitations of screen
    • False negative vs false positive
    • carriers
  – Adequacy of genetic service infrastructure
  – PH infrastructure for proper gender assignment
DMD ELSI WG

WG will provide specific recommendations for:

1. Future study of ELSI issues (e.g. what a pilot could do)

2. What a state NBS program should do once DMD makes the RUSP (e.g. screen only for boys)