

# Ethics of Genetic Research in Infants, Children, and Adolescents

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## Research in Children

- Has been a process of evolution
- Declaration of Helsinki in 1964
  - Must have potential diagnostic and therapeutic value for the participant
- Revised Declaration of Helsinki
  - Research is necessary to promote the health of the population represented (same age and condition represented by the subjects)
- European Convention on Human Rights and Biomedicine in 1997
  - Inclusion of minors if there is minimal risk
- Guidelines of the Council for International Organizations of Medical Sciences
  - May not necessarily directly benefit from the research (need not be the same age or condition)

## Conflict of Interest in Genetic Research in Children

- May identify susceptibility to disease for other family members
- May identify a heritable trait that would be associated with guilt by one or both parents
- May identify non-paternity

## Important of Including Children in Genetic Research

- If children are not enrolled in genetic studies of minimal risk we will be unable to understand genetic susceptibility to pediatric diseases and pharmacogenetics

## Risks of Genetic Testing/Genetic Research for Highly Penetrant Conditions

- Psychological
- Social-stigmatization
- Discrimination-health insurance, life insurance, job security
- Because of these risks the AAP does not recommend genetic testing for children unless it has immediate medical implications for them (confirming a diagnosis, medical intervention as a child, carrier testing for teens who are pregnant)
- Genetic testing for adult onset disorders with no effective pediatric intervention is recommended against (ie *BRCA1/2* and Huntington Disease)

## Newborn screening

- Clinical programs in newborn screening
  - Designed to identify conditions for which there is acceptable treatment that will prevent long term medical problems and death from diseases that are otherwise not readily apparent at birth
  - PKU and hypothyroidism are classic examples

## Newborn Screening

- Experimental programs in newborn screening: pushing the envelope to include conditions for which there is no proven clinical efficacy of early identification of children with highly penetrant diseases (ie cystic fibrosis)
- Unselected large population facilitates many types of genetic studies
- Some states (Massachusetts) have adopted programs to allow parents to participate in supplemental experimental newborn screening for CF and additional inborn errors of metabolism (uptake is > 95%)

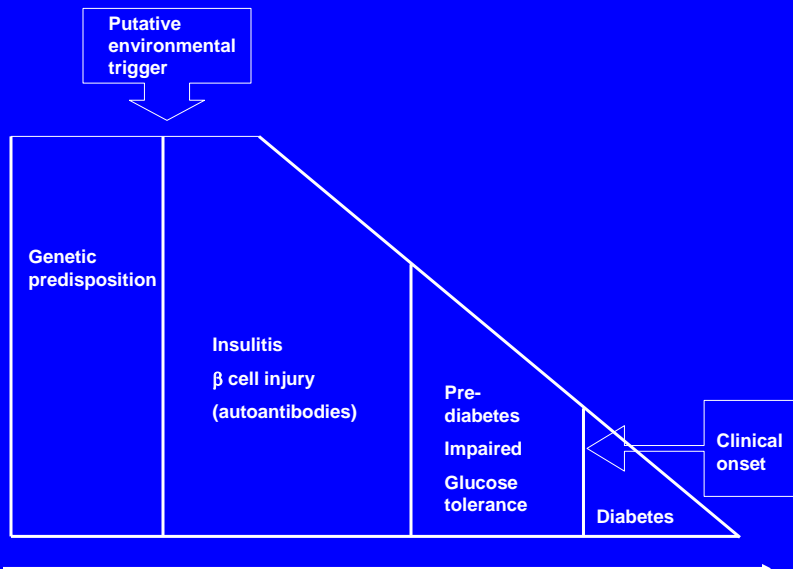
## Risks of Newborn Identification of a Highly Penetrant Genetic Condition

- Decreased parental bonding
- Adoption of an immediate sick role
- Burden of false positives
- Guilt

## Should the Infrastructure of Newborn Screening Be Used for Experimental Studies?

- Enrollment is high (>94%)
- But do parents provide *informed* consent?
- Should research studies be performed only on an anonymous basis without disclosure of results?
- Should the experimental studies be separated from NBS to
  - Allow clinical from research newborn screening to be differentiated?
  - Force parents to actively participate and increase likelihood for being informed?
  - Increased cost of such design and decreased accrual

## Natural History of T1DM



# Genetic Susceptibility of T1DM

DR/DQ	Risk	
	First-degree relative with diabetes	General population
DR 3/4, DQ 0201/0302	1/4-5	1/15
DR 4/4, DQ 0302/0302	1/6	1/20
DR 3/3, DQ 0201/0201	1/10	1/45
DR 3/X, DQ 0302/X (X ≠ 0602)	1/15	1/60
DR 0403 or DQ 0602	1/15,000	1/15,000

## Pediatric Screening for Genetic Susceptibility to Type 1 Diabetes

- Multifactorial Disease
- HLA-DQB1 identifies an at risk haplotype with an 8% risk of developing T1DM
- Genetically at risk can be followed with autoantibodies for progression to T1DM (requires disclosing results to participants)
- May identify environmental exposures necessary for development of T1DM (infectious etiologies, cow's milk)
- No methods of prevention are available

## Pediatric Screening for Genetic Susceptibility to Type 1 Diabetes

- How should studies be designed?
- Population based screening?
  - DAISY (Diabetes Autoimmunity Study in the Young)
  - PANDA (Prospective Assessment in Newborns for Diabetic Autoimmunity)
  - 90-94% of mother's consent
  - Positive results produced great parental anxiety which persisted and was extreme in certain groups
- High risk screening (first degree relatives of T1DM who are already at 10 fold increased risk)?
  - Only accounts for 10% of T1DM
  - Factors may be different than non-familial cases
  - Parents are more likely to provide *informed* consent
  - May relieve anxiety if child who was thought to be at risk is found to be at lower risk

## Pediatric Screening for Genetic Susceptibility to $\alpha$ 1 Antitrypsin Deficiency

- Autosomal recessive condition with variable penetrance and expressivity leading to severe pulmonary disease in young adults
- Condition exacerbated greatly by smoking and second hand smoke
- Screening was performed on newborns in Sweden in 1970's
- Recruitment was stopped due to psychological stress (especially of mothers) within positive families
- As young adults, the affected children thought positively about study participation

## LEGACY (Lessons in Epidemiology and Genetics of Adult Cancers in Youth)

- Longitudinal study of girls ages 5-18 with familial breast cancer (many are BRCA 1/2 carriers) to determine environmental factors that may influence risk of breast cancer development (especially diet, exercise, body weight, puberty)
- Requires longitudinal questionnaires, physical examinations, and blood samples
- Genetic testing will be performed, but results will not be disclosed to study participants. All participants will be followed in the same manner
- Pilot studies indicate parents are interested in having their daughters participate in research, but parents vary in when and how much information should be disclosed to their daughters and what tests they/their daughters would find acceptable

## LEGACY-Potential Harm

- Girls being forced to recognize their potentially increased risk of breast (ovarian) cancer at a young age and during formative years
- Some girls will be disproportionately affected
- When should girls provide assent during a longitudinal study?
- What if parents' opinions differ about daughter's enrollment?
- What if the mother's/relative's status changes during the study (ie recurrence, second primary, death) and the daughter's perception then changes?



## Who should provide consent?

- One parent?
- Both parents?
- Legal guardian for children in foster care?

## Children Should Participate in Consent/Assent When Appropriate

- How does one determine ability to give assent for complex genetic studies?
- Should genetic counseling be provided?
  - If requested, absolutely.
- Should minors give consent once they reach majority?