

Carrier Screening

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Disorders in Newborns and Children

Objective of project and presentation

- Brief review of the issue
- What do we already know?
- Review current status of carrier project
- Outline proposed plan of action
- Proposal for the joint task force approve or disapprove

What do we mean by carrier screening?

- Detection of people who are carriers of a gene mutation for a recessive disorder
- People at risk for having an affected offspring for a life threatening autosomal recessive disorder
- Can be deliberate or incidental (through technology as in newborn screening for hemoglobinopathies)

Examples of possible carrier screening:

- Common mutations, founder effect
 - CF, Sickle cell, Gaucher
 - Limb girdle dystrophy 2B, Fukuyama muscular dystrophy
- High mutation rate, widely distributed new Mutations- sequencing
 - DMD, NF, TS

Some Considerations for Carrier Screening

1. Disorder impairs health in the homozygous affected offspring.
2. High frequency of carriers in the screened population
3. Technically and clinically valid screening methods are available
4. Screening methods are efficacious.
5. IVF, prenatal diagnosis and termination are options.
6. Consent (informed and voluntary participation) is protected.
7. Knowledge of benefit and harms for carrier testing is transmitted to the screenee, both pre and post testing.
 - Anxiety over probabilistic results is minimized.
8. Privacy is protected (non- discrimination for insurance and job).
9. Stigmatization of the carrier by the community is minimized.
10. Experienced professional resources are required.

Perspectives to consider

- Public Health
- Clinical specialty and primary care practices
- Current screening programs
- Carrier detection as part of newborn screening
- Family and Individual perspectives

Issues Identified:

- Who to screen?
 - Population screening
 - High risk population screening
 - Targeted screening if indications from history
- How to screen?
 - Family history
 - Genetic testing
 - Blood spot
 - Biochemical markers

Timing of Screening (When)

- Newborn screen for carrier status
- Childhood screening-
 - at time of other mandatory testing
 - I.e. lead and hemoglobin levels
- At age 18 years
 - Age of consent
- Planning pregnancy
- Already Pregnant

What is the purpose of the screen?

- Inform reproductive choices
- Carrier status has health impacts- OTC carrier, LCHAD carrier, SC trait, Fabry
 - When no other interventions can avoid problems or problems that impact only those who are carriers
- Other reasons?

Re-screening?

- Identified early as carrier- (newborn screening)
 - will this information stay with them for informing reproductive choices or health interventions
- Who is responsible for counseling?
- When should this counseling be done?
- Who should be targeted for rescreening?

Direct to consumer testing

- Commercial panel being offered to consumers
- Who is making sure the testing is done according to professional (AAP, ACOG, ACMG) guidelines?
- Who is responsible for counseling?
- What is adequate counseling?
- Who is responsible for keeping the information for later time when considering reproduction?

Previous experiences

- CF prenatal screening- CA experience
 - Less than 50% of OBs offered to patients
 - Less than 17% of couples were offered prior to universal NBS for CF- this improved after implementation
 - The panel to screen for is growing, depends on accurate assessment of ethnic background
 - Results may be discrepant between prenatal and NBS results

Previous experiences

- Preconceptional screening- the Ashkenazi Jewish experience
 - 1 test recommended in 1973 (Tay Sachs)
 - Started with enzyme, moved to DNA in 1990
 - In 2008 recommended panel was 9 disorders- but possible to do mutation analysis for 16 disorders with known founder mutation

Previous Experiences

- Sickle Cell disease
 - AIR FORCE POLICY ON TRAIT CARRIERS (1970s); UREA DEBACLE AND SEARCH FOR DESICKLING AGENTS
 - Stigma related to being carrier- NCAA policy
- Negative impact of detecting carriers
 - *Rowley: NY State J Med 1986;141593; Am J Dis Child 1979;133:1248; Am j Dis Child 1983;137:341; Science 1984; 225:138.*
 - Stigmatization
 - Reduced maternal bonding
 - Discrimination

Recent Meetings:

- CARRIER TESTING FOR SPINAL MUSCULAR ATROPHY
 - NIH 2009
- POPULATION-BASED CARRIER SCREENING FOR SINGLE GENE DISORDERS: LESSONS LEARNED AND NEW OPPORTUNITIES
 - February 6-7, 2008- meeting in Rockville, MD
- Genetic Carrier Screening: Moving Population Genetics from Theory to Practice (HRSA sponsored)
 - Nov. 20, 2006 Bronx, NY

Previous Meetings' Conclusions:

February 6-7, 2008 Rockville, Maryland

- ***What to screen for and when to screen?
Developing criteria for disorder selection in
the setting of economic and social
constraints.***
 - The top three considerations should be carrier frequency, disease burden, and cost of screening.
 - What to screen for depends on the rationale for screening, i.e., what actions can be taken and when would screening occur across the life spectrum?

- ***How should we balance the screening interests of individuals, communities, and society?***
 - The first order principle is to *engage the relevant communities*. While consumer-driven special interest might be major force, the medical model is an equally significant force; thus, *identifying the rightful gatekeeper is challenging*.
 - *Other screening models* to consider in developing criteria are imaging, cholesterol, blood pressure, and obesity, as indicators of future disease. Immunization policy and seatbelt laws are public health models that bypass individual interest in favor of public health and societal interests.

- ***Should services be targeted to subpopulations? If so, on what basis can subpopulations be accurately identified? Balancing science, ethics, and clinical utility.***
 - A key consideration *is when to address targeting issues*—at the time when screening is offered or when interpreting the results of screening. If you cannot categorize people on the front end of screening, you can at least customize the interpretation on the back end.
 - The *community should drive what is offered*, but defining community is difficult—is it ethnicity, self-identity, or based on scientific markers? Another way of defining community is through point of service (e.g., newborn, prenatal)
 - *Subpopulations* should be targeted only if population characteristics (e.g., reproductive isolates, specific geographic origin of ancestors) justify such an approach.

- ***How is informed consent defined and obtained?
Models for multiple complex tests applied to the
general population***

- Key elements of informed consent for carrier screening include: the *meaning of the term carrier*, its meaning to you and your family, risks and potential benefits of the information, where to get follow-up information, *levels of uncertainty* about the test, and the future of the disease. These elements become more complex with the use of multiplex tests.

- ***How can we measure the success of carrier screening programs? Developing an evidence base.***
 - Methods for measuring success include: evaluations of pre- and post-testing education; surveys to determine whether tests are being appropriately offered; assessment of opt-in and opt-out rates; costs per net health benefit measurements; qualitative measures of “choice” in carriers and the general population (individuals who are screen negative); evaluations of enhanced genetics competency of health professionals; cohort studies (follow-up of screened populations) for rare diseases; population-based studies for other conditions; community-based research (e.g., public consultation).

November 19, 2006, “Genetic Carrier Screening: Moving Population Genetics from Theory to Practice”

- Need standardization of criteria for selection of population-based screening tests
- Need to understand the burden and natural history of each condition, the inheritance and carrier frequency, and genotype-phenotype correlations.
- Fundamental questions about the performance of tests (e.g., true positives and false positives) and how one’s follow-up results must be considered.
- Need to ensure laboratory reports are simple and understandable

- In light of the success of CF carrier screening a similar model could be adapted for SMA carrier screening in the future.
- There are other Jewish populations and other endogamous non-Jewish populations at risk for other serious genetic conditions.
 - These populations might be candidates for ethnic-specific, as well as panethnic testing panels.
- *Models for earlier preconception or childhood screening should be undertaken and funded*
 - understanding that the positive impact can be maximized through grassroots and community-based initiatives.

- Other suggestions to improve care include providing NBS test results to all parents of children who screen positive for hemoglobinopathy carrier status
 - ensuring that sickle cell test results become part of all students' health records.
- The mandatory nature of newborn screening often puts Latinos in an unwanted position, suggesting that customized counseling is very important.
 - Education, in a broad sense, will probably be the cornerstone for success for future policy design and implementation.
- Case law has set a precedent for antidiscrimination in relationship to genetic testing, there are still some areas where things are not as clear-cut, such as duty to disclose
- It is essential to be very thoughtful as guidelines are developed and to seek the input of both professionals and community members

NIH Meeting on Carrier Screening for SMA

- Pan-ethnic carrier screening for SMA is technically feasible and that the specific study of implementing an SMA carrier screening program raises broader issues about determining the scope and specifics of carrier screening in general.
- **The consensus of meeting participants was that in order to effectively address the broader issues affecting many diseases, including SMA, a federal process such as that begun by the SACHDNC will be needed to balance stakeholder interests, values, and ethical considerations in making recommendations on carrier screening programs.**
- **Recommended that SACHDNC work with SACGHS to pursue carrier screening issues more broadly**

Summary

- Some work has been done previously
- Some populations have been very successful with carrier screening
- There is no model for population-based carrier screening
- There are many issues, and probably no right answers to all of them.
- Deciding which conditions should be screened, and when, is difficult at best.

Plan Outline

- Present to SACHDNC- May 2010
 - Get feedback and possible proposal for task force development
- Present to SACGHS- June 2010
 - Discuss role of a task force
- Convene joint workgroup to:
 - Propose purview
 - Propose activities
 - HHS workshop?
 - IOM meeting?