

LITERATURE REVIEW OF PRECONCEPTION EXPANDED CARRIER SCREENING

[ACOG committee opinion on CF screening](#) 2011; reaffirmed 2014

- Preconception carrier screening gives couples time to consider the most complete range of reproductive options
- Knowledge of risk may influence a couple's decision to conceive or to consider IVF with PGD, prenatal testing or use of donor gametes.
- CF carrier screening should be offered to all patients (as opposed to earlier guidelines only recommending it for Caucasians) because "it is becoming increasingly difficult to assign a single ethnicity to affected individuals."

[Expanded Carrier Screening Reproductive Medicine-](#) Points to Consider, Am Jour Ob Gyn 2015

- Joint statement by the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal Fetal Medicine
- "Whether the practitioner follows current professional society recommendations or uses expanded carrier screening, the goal of preconception and prenatal carrier screening is to provide couples with information to optimize pregnancy outcomes based on their personal values and preferences."
- Ancestry-based screening has limitations, including inaccurate knowledge of ethnicity and the recognition that genetic diseases do not occur solely in specific ethnic groups.
- Post-test counseling / patient education is an important component of carrier screening.
- Appropriate considerations for offering expanded carrier screening are defined as: a) women of reproductive age before conception; b) egg and sperm donors; c) preconception screening can be offered sequentially or in tandem (both partners at the same time) but for pregnant couples, it makes more sense to screen both parents at the same time.

[A Re-Examination of the Use of Ethnicity in Prenatal Carrier Testing](#) Am Jour Med Gen 2011

- ACOG needs to apply its CF screening policy to all diseases, thereby eliminating reliance on self-reported ethnicity
- Carrier screening should follow the model of newborn screening, where diseases are chosen because of clinical severity or actionability, rather than prevalence in a certain ethnic group
 - As an example of the unreliable nature of ethnicity, over 1000 babies identified with sickle cell disease (through California newborn screening programs 1990-94) were Caucasian
- "...there are many reasons why women or couples fail to provide a fully accurate ancestral history including the fact that many do not know their family trees and that most of us have more admixture than we realize. Finally, the objection to universal screening for a wide array of conditions will lose any remaining legitimacy when new technologies provide multiplex testing easily and cheaply."
- Informed decision-making begins with awareness

[The Future is Now - Carrier Screening for all Populations](#) Genetics in Medicine 2008

- "...as more diseases are added to [Ashkenazi Jewish] panels, some carrier states in the targeted populations begin to approach the prevalence in the general population leading one to consider whether it is more appropriate to employ panethnic screening panels for these conditions rather than subpopulation-targeted panels.
- "Variable carrier rates in broad populations make race/ethnic-based recommendations even more difficult to develop (i.e., the carrier pending on country of origin) such that panethnic testing may become a more viable option in the forever changing American landscape."

- “...there remain some challenges and opportunities, with a suggestion that physicians, other health care providers, and consumers still need additional education about screening, including the meaning of a negative or positive test result.”

[Psychosocial Impact of Living as a Carrier](#) Journal of Genet Couns 2011

- Systematic review of 20 studies performed over a period of 10+ years
- No significant difference in anxiety between carriers and non-carriers
- Initial anxiety in carriers dissipates after 6 months, usually owing to adequate genetic counseling
 - Author speculation: “...another reason may have been because none of the participants were pregnant at the time of receiving their carrier test results and were therefore not anxious about the possibility that the fetus was affected.”
- Emotions differed between those carriers who already had an affected child and carriers who did not. Carriers with affected children were more likely to experience guilt.

[American College of Medical Genetics Position Statement on Expanded Carrier Screening](#) 2014

- Cost is no longer a barrier to adoption, so other criteria must be explored
- Basic criteria should be met when determining what diseases to include on a panel. High-level summary of criteria below:
 - a. disease is of a nature that parents would consider prenatal diagnosis
 - b. adult-onset disorders require specific consent
 - c. causative genes, mutation frequency and residual risks are understood
 - d. clinical association between mutation and severity of disease is validated
 - e. laboratory is compliant with ACMG standards and guidelines

[Current Controversies in Prenatal Diagnosis - Expanded Carrier Screening](#) Prenatal Diagnosis 2014

- Question posed by authors: Should preconception expanded carrier screening replace all current prenatal screening for specific gene disorders?
- Arguments in favor:
 - cost is low and therefore accessible
 - ethnicity is a nebulous concept
 - broad-based preconception maximizes reproductive choices and offers a non-discriminatory approach to risk assessment
 - all young adults should be routinely offered and public education should ensue
 - preconception minimizes ethical dilemma of termination as the only option
- Arguments against:
 - Thirty-one percent of pregnancies in the US are unplanned; preconception *only* screening will miss many women of reproductive age
 - It's not clear what disorders to include, and it's currently left to the discretion of the lab, physician or patient. ACMG criteria stating that disease “should be of a nature that parents would consider prenatal diagnosis” is too vague.
 - There is a tremendous hurdle to curate, maintain and report all mutations associated with a specific phenotype
 - Educational burden is high and the “underlying commitment to education” has not been adequately addressed in guidelines

[Changing Landscape of Carrier Screening](#) Journal of Law Medicine: 2013

- Forty genetic professionals participated in six focus groups for this study.
- Concerns about obtaining adequate informed consent emerged from the group

- "...issues regarding the integration of genetic risk information into reproductive health care and are not unique to ECS [expanded carrier screening] technology."
- Authors acknowledge that preconception carrier screening is recommended by medical professional societies but logistically challenging because of unplanned pregnancies
- "Empirical research suggests that pregnancy itself is a lens through which women make decisions about whether to accept carrier testing, whereby "underlying belief systems, heightened vulnerability and personal stress management strategies" influence decision-making during pregnancy."
- "The inclusion of more disease risks in CS [carrier screening] panels brings with it the increased possibility that more pregnant women will receive positive results, potentially making identification as a carrier 'the new normal.'"

[Carrier Screening for SMA](#) American Journal of Medical Genetics: 2010

- As background, ACMG recommends screening for spinal muscular atrophy (SMA) while ACOG does not; this discordance in guidelines leaves screening to the discretion of a provider
- SMA is the leading genetic cause of infant death under the age of two
- The authors argue that population-based carrier screening for SMA (as with cystic fibrosis) allows couples to make "informed reproductive choices"
- The carrier rate of spinal muscular atrophy in the general population approximates 1/54

[We Screen Newborns, Don't We? Realizing the Promise of Public Health Genomics](#) Genetics in Medicine: 2013

- This is an opinion piece, not necessarily specific to carrier screening before pregnancy, about the implementation of genetic screening as a public health tool; author is highly-regarded in the field
- Millions of people in the US unknowingly carry mutations for rare but preventable diseases
- A benefit of focusing on rare disease is the identification of other at-risk family members (siblings, cousins, etc) who otherwise would have no knowledge of their carrier status
- Widespread screening could cause anxiety but this is no different from other well-established public health screening tools that assess future risks, like cholesterol analysis, cervical dysplasia or blood pressure tests

[Genetic Counseling and Testing for FMR1 Gene Mutations: Practice Guidelines of the National Society of Genetic Counselors.](#) J Genet Counsel (2012) 21:752-760.

- FMR1 testing for Fragile X syndrome is 99% sensitive
- As background: the average age at diagnosis is 3 years. By that time, the parents could already have another child on the way with a significant risk for a condition that is entirely detectable preconception. Fragile X is the most common inherited cause of mental retardation.
- "General population studies of FMR1 testing in women have demonstrated its efficacy and cost effectiveness (Musci and Caughey 2005). Voluntary screening for FMR1 mutations appears to be acceptable to women in the general population and to the parents of affected children (Bailey et al. 2003; Hill et al. 2010)."
- Pre- and post-test counseling should be available

[Obstetricians and Gynecologists Practice and Opinions of Expanded Carrier Testing and Non-invasive Prenatal Testing](#) Prenatal Diagnosis 2014

- Survey of 621 ob/gyn professionals
- Challenge is around whom to offer screening and what counseling should be included

- Of participants, 80.2% considered the ideal time for carrier screening to be either in early adulthood (14.4%) or as part of preconception family planning (65.8%).
- Professional and public education is necessary in order shift the timing of screening away from prenatal and toward preconception