

Prenatal Genetic Carrier Screening

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Prenatal Carrier Screening

Objectives, overview:

- Current practice recommendations
 - Review current screening recommendations
 - Controversies in carrier screening
 - Fragile X Screening
 - Spinal Muscular Atrophy (SMA)
 - Universal or Expanded Carrier Screening

Screening Approaches

Screening for
Carriers

Prenatal

Screening for
Affected

Newborn

Conception

20 wks

Birth

Practice Guidelines

- ACOG and ACMG (the American College of Medical Genetics) both provide recommendations for prenatal screening of specific genetic diseases
- In several situations, the guidelines are different

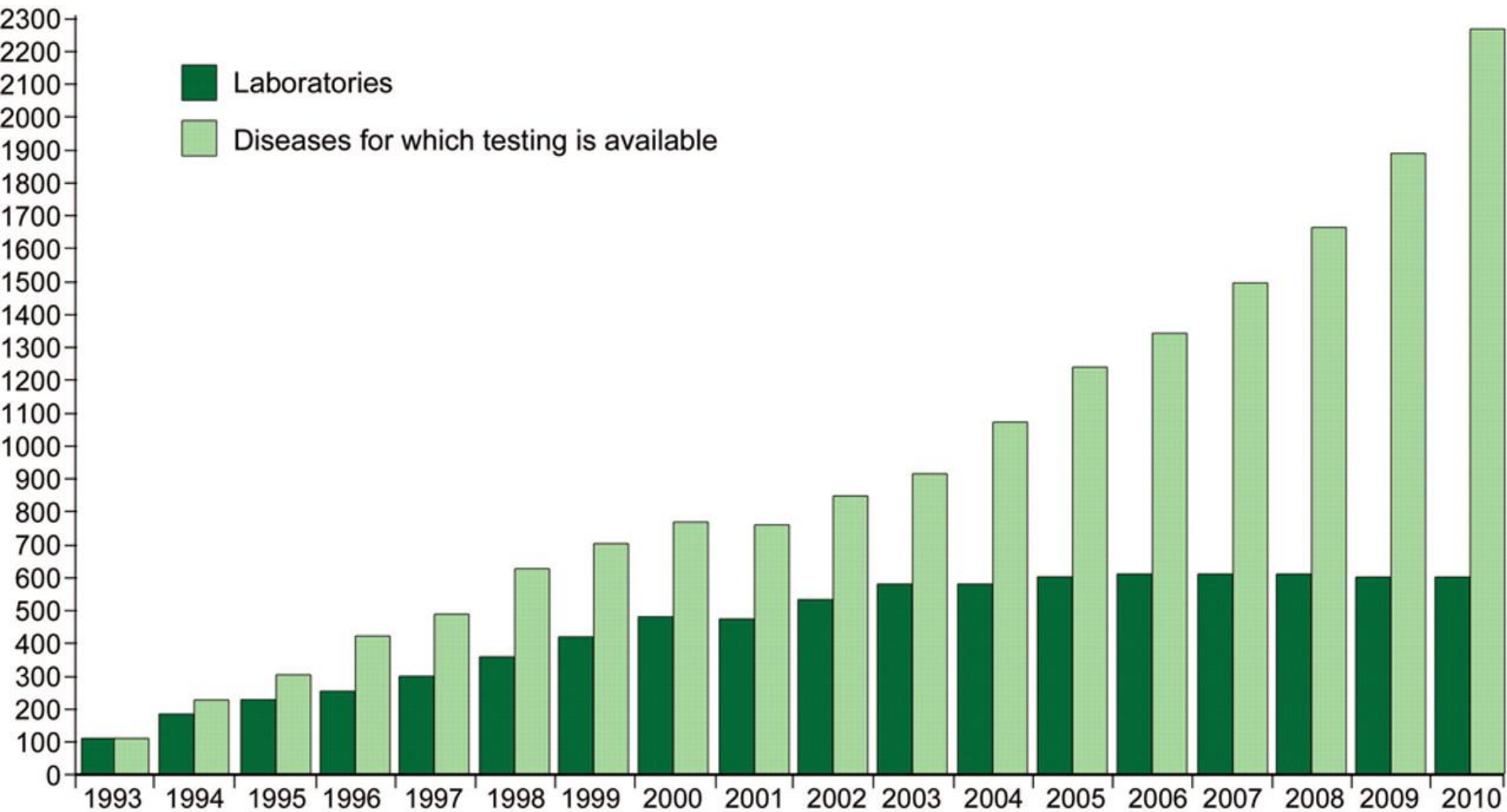
Genetic Diseases are Not as Rare as we Think!

2-3% of newborns have a congenital disease or malformation

These result in:

- More than 20% of infant mortality
- 30% of ICN admissions

Increase in available genetic tests



Data source:  Tests database (2010/www.genetests.org)

Carrier screening

Goal is to identify asymptomatic carriers with no family history of disease

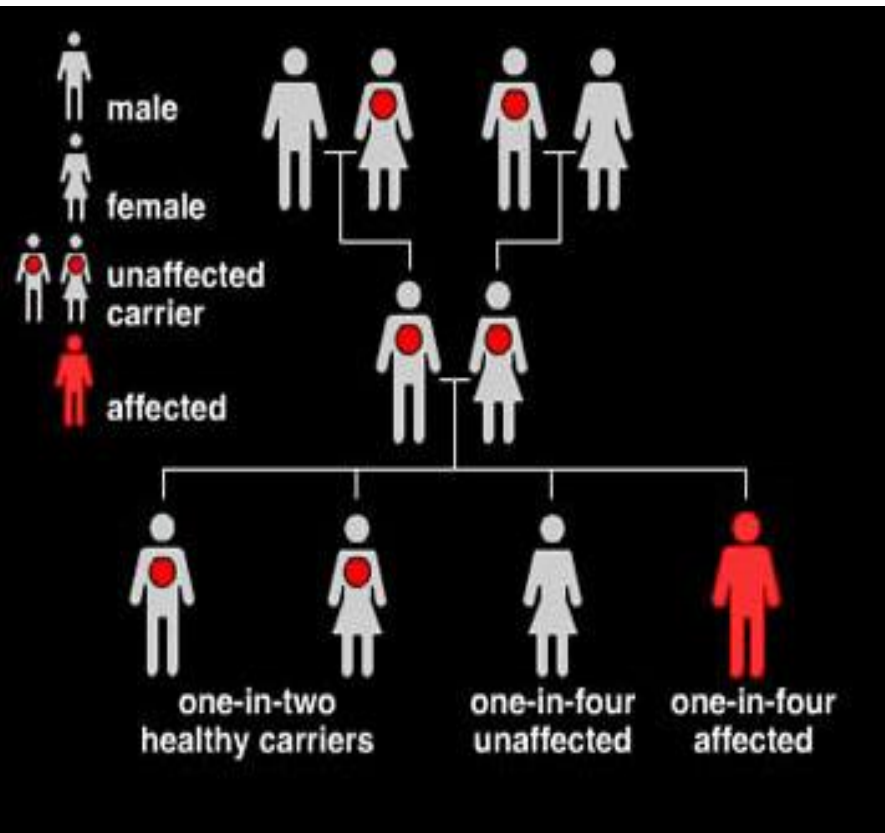
As more tests become available, questions arise:

- Which should be offered?
- Who should decide?
- Who should pay?
- What is our medico-legal and ethical responsibility?

Heterozygote (Carrier) Screening

Most are autosomal recessive disorders

- Carriers typically asymptomatic
- Usually no family history
- Affect males and females equally
- Risk for carrier parents to have an affected child is $1/4$ for each pregnancy



Ethnicity-Based Screening

- Frequency of many disorders varies among ethnic groups
- Effectiveness of screening also varies by ethnicity
 - Different populations have different mutations that cause the disorders
 - Testing usually targets the commonly affected groups, less effective in non-target populations

Ethnicity Based Screening

Ashkenazi Jewish

Tay Sachs disease, Canavan disease, cystic fibrosis, familial dysautonomia

Louisiana Cajun,
Fr Canadian

Tay Sachs disease

Caucasian

Cystic fibrosis

Africans, African
American

Sickle cell anemia, beta
thalassemia

Southeast Asian

Alpha thalassemia

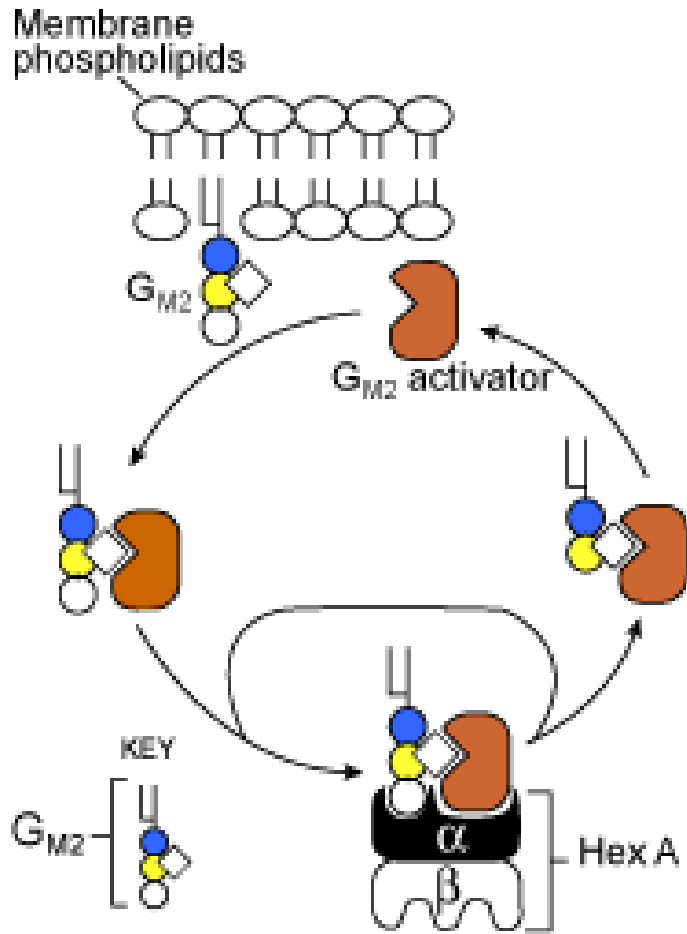
Mediterranean

Beta thalassemia

Ethnicity Based Screening

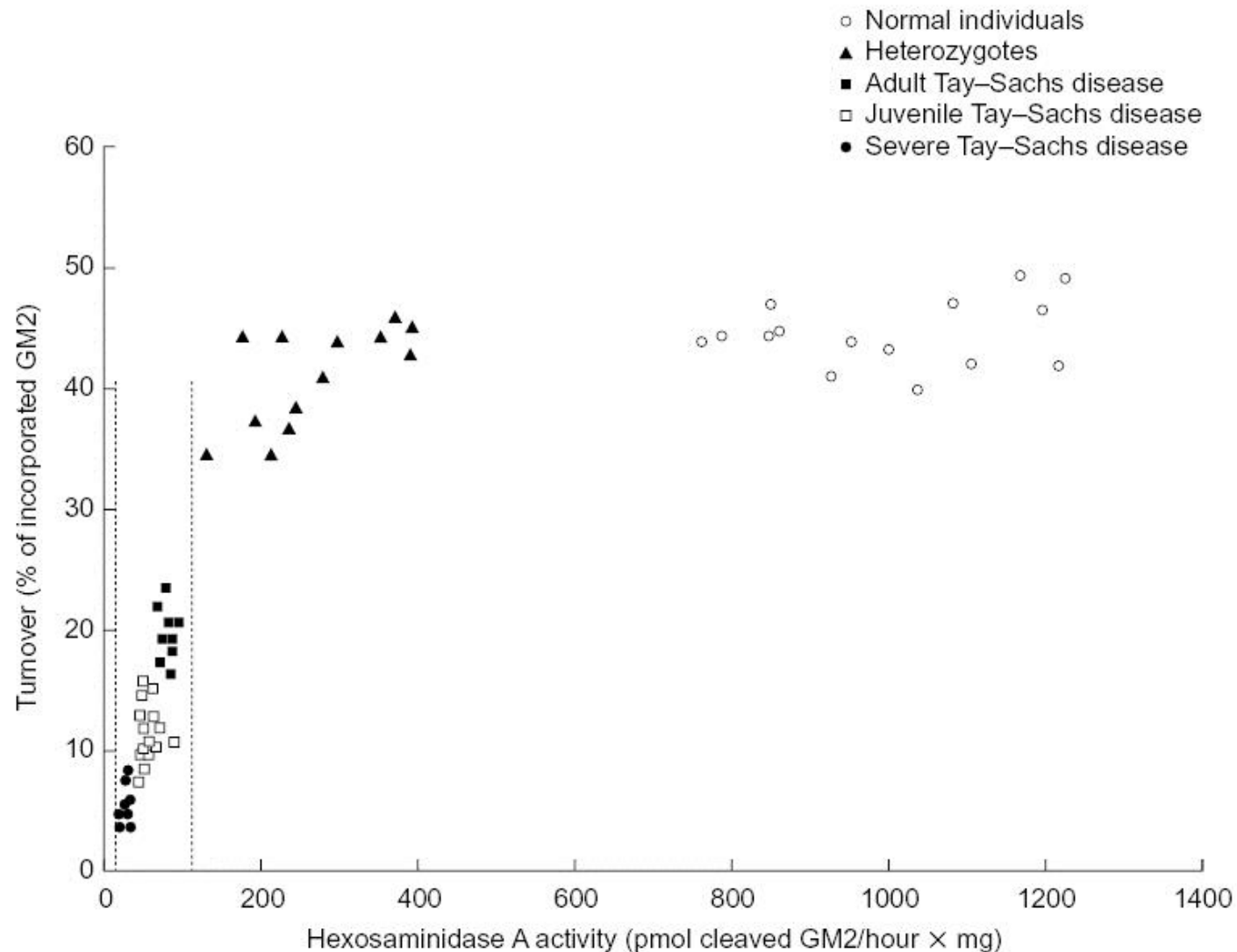
- May present barriers by requiring knowledge of who to screen for which disorders
- Perpetuates categorizing of patients by race and ethnicity
 - Can be seen as stigmatizing
- Less robust with increasing multiculturalism
 - Less clear how to assign patients to a single ethnic or racial group in modern society

Tay Sachs Disease



- TSD is a lysosomal storage disease caused by hexosaminidase A (hex A) deficiency
- Resultant accumulation of GM2 gangliosides results in progressive neuro-degeneration
- Death in early childhood
- There is no treatment or cure

Hex A Activity in Tay Sachs Disease



Ashkenazi Jewish Screening

- Screening for Tay Sachs disease was one of first public health genetic programs
- Carrier screening has resulted in dramatic decrease in frequency of TSD in this group

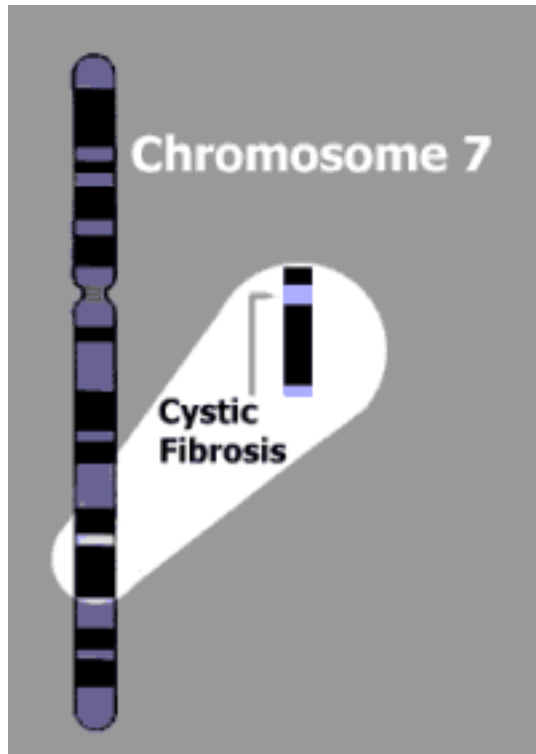
Enzyme assay vs DNA?

- Initially screening involved enzyme assay for Hexosaminidase A activity
- More recently, a DNA test was developed
- Both have good sensitivities and specificities, although neither is perfect
- *Enzyme screening is better for non-Ashkenazi Jewish individuals and perhaps all*
- In complex cases, a combination of tests may be required

Cystic Fibrosis

- Most common autosomal recessive disorder among Caucasians (1/3300)
- ~1/25 Caucasians *with no family history* is a carrier of CF
- 80% of children with CF are born to parents with no prior history of the disease

Cystic fibrosis transmembrane conductance regulator gene (CFTR)



- Defective chloride transport->high sweat chloride levels
- Tenacious mucous in lungs and pancreas-> severe pulmonary disease, pancreatic insufficiency, malabsorption
- *Wide range of severity, although most die of pulmonary disease at mean age of 37 (2006)*

Testing for CF by genetic mutation analysis

- Nearly 2000 gene mutations identified
- Standard recommendation is a 23 mutation panel
 - Detects 94% Ashkenazi, 88% other Caucasian carriers
 - Detection rate and prevalence of disease both lower in other ethnic groups

CF Detection Rates and Carrier Risks*

<u>Group</u>	<u>Carrier risk</u>	<u>Detection rate</u>	<u>Carrier risk w/neg test</u>
Ashkenazi	1/24	94%	1/380
Caucasian	1/25	88%	1/200
Hispanics	1/58	72%	1/200
African-Am	1/61	64%	1/170
Asian-Am	1/94	49%	1/180

*Risks only apply with NEGATIVE family history!

ACMG 2010

CF genetic mutation analysis

- Original recommendation for 25 mutation panel
 - Present in at least 0.1% of cases of classical CF
 - Goal to screen for severe, classical phenotype
- With experience, 2 mutations removed as they caused mild or atypical disease
- Adding additional mutations is of limited benefit, as each new mutation typically rare
- Rare mutations are often of uncertain clinical significance

CF mutation analysis

- Many of these additional mutations:
 - Are rare
 - Cause mild or atypical CF (sinusitis, nasal polyps)
 - Cause uncertain phenotype
 - Add little to detection rate
 - Increased detection almost entirely due to mutations that are inconsequential or of uncertain significance
- 100 mutations is NOT 4 times better than 23!

Rohlfes et al, Clin Chem 2011; Strom et al, Genet Med 2011

Fragile X Syndrome

A



B



C



- Most common inherited form of mental retardation
 - MR, joint laxity, tall stature, large jaw, characteristic faces, hyperactive behavior
- Most common single gene defect associated with autism
- 1/4000 males and 1/8000 females affected
- Carrier frequency 1/157

Berkenstadt et al, 2007

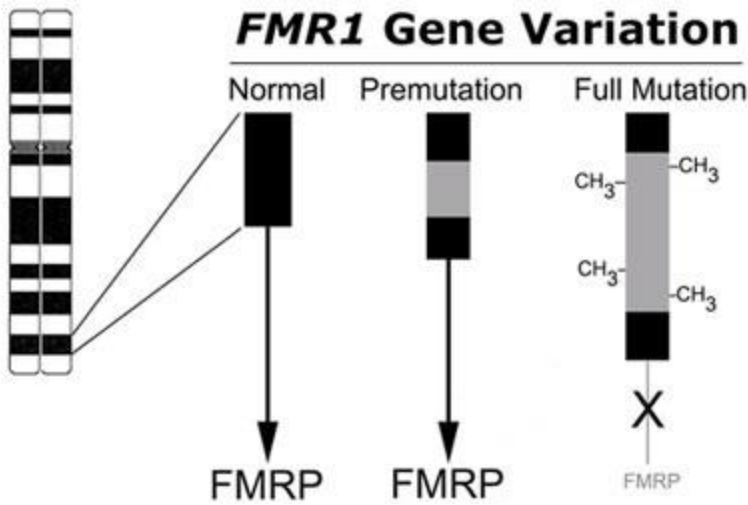
Fragile X Syndrome: Other features

Associated with a broad spectrum of clinical features:

- Late onset tremor/ataxia syndrome
- Premature ovarian failure
- Female infertility
- Psychiatric disease
- Autism

Fragile X Syndrome

- At present, population screening is not recommended
 - This is being debated
- Common form of MR, genetic test available, severe phenotype
- But the genetic counseling is complex



Fragile X

- Carriers have a “premutation” that can expand to a “full mutation”
- Full mutation in males and some females causes fragile X syndrome
 - Outcome in females is unpredictable, from typical fragile X syndrome to a normal outcome

Spinal Muscular Atrophy

- Severe hereditary neuromuscular disorder
- Autosomal recessive
- Second most common severe autosomal recessive disorder after cystic fibrosis
- Most common inherited cause of early childhood death
- ~1/10,000 live births, 1/40-60 carrier frequency

Complexities of Carrier Testing for SMA

- Negative screen reduces but does not eliminate risk (detects ~90%)
- Complexities of molecular testing and interpretation
 - Lack of genotype/phenotype correlation
 - Type 1 (most severe) accounts for 70% of cases, type II and III for 30%; carrier testing does not predict type
- Difficulties in providing genetic counseling services

Practice Guidelines: Spinal Muscular Atrophy

ACOG + ACMG have quite different opinions on SMA screening

ACMG:

- Carrier testing should be offered to all couples regardless of race or ethnicity

ACOG:

- Screening for SMA is not recommended for general population
- Screening should be offered to those with a family history of SMA, or if requested, after genetic counseling

Multiplex Panel Screening: Universal Screening

- Multiplex screening now allows testing for many (>100) disorders at once
- This is relatively inexpensive (\$99)
- Should it be offered to everyone?

One Test for 100+ Genetic Diseases

[Register Now](#)

Each year, millions of unsuspecting couples are at risk for conceiving a child with a serious genetic disease, such as [cystic fibrosis](#), [spinal muscular atrophy](#), [fragile X](#), or [Tay-Sachs disease](#).

While these diseases cannot be cured, with the [Universal Genetic Test](#) they can now be [prevented](#). The test is recommended to be offered to both men and women and tests for diseases common to every [ethnic group](#), for maximum safety.

Learn more about each of the diseases covered by the test below.



Full Disease List

ACOG = Testing for this disease recommended to be offered by ACOG

ACMG = Testing for this disease recommended to be offered by ACMG

[ABCC8-Related Hyperinsulinism](#)

[Achromatopsia](#)

[Alkaptonuria](#)

[Alpha-1 Antitrypsin Deficiency](#)

[Alpha-Mannosidosis](#)

[Andermann Syndrome](#)

[ARSACS](#)

[Aspartylglycosaminuria](#)

[Ataxia With Vitamin E Deficiency](#)

[Ataxia-Telangiectasia](#)

[Autosomal Recessive Polycystic Kidney Disease](#)

[Bardet-Biedl Syndrome, BBS1-Related](#)

[Bardet-Biedl Syndrome, BBS10-Related](#)

[Biotinidase Deficiency](#)

[Bloom Syndrome](#) **ACMG**

[Canavan Disease](#) **ACMG** **ACOG**

[Carnitine Palmitoyltransferase IA Deficiency](#)

[Carnitine Palmitoyltransferase II Deficiency](#)

[Cartilage-Hair Hypoplasia](#)

[Choroideremia](#)

[Citrinemia Type 1](#)

[CLN3-Related Neuronal Ceroid Lipofuscinosis](#)

[CLN5-Related Neuronal Ceroid Lipofuscinosis](#)

[Cohen Syndrome](#)

[Congenital Disorder of Glycosylation Type Ia](#)

[Congenital Disorder of Glycosylation Type Ib](#)

[Congenital Finnish Nephrosis](#)

[Costeff Optic Atrophy Syndrome](#)

[Cystic Fibrosis](#) **ACMG** **ACOG**

[Cystinosis](#)

[D-Bifunctional Protein Deficiency](#)

[*Factor V Leiden Thrombophilia](#)

[Factor XI Deficiency](#)

[Familial Dysautonomia](#) **ACMG** **ACOG**

[Familial Mediterranean Fever](#)

[Fragile X Syndrome Type 1](#) **ACMG**

[Hexosaminidase A Deficiency \(Including Tay-Sachs Disease\)](#) **ACMG** **ACOG**

[*HFE-Associated Hereditary Hemochromatosis](#)

[Homocystinuria Caused by Cystathionine Beta-](#)

[Synthase Deficiency](#)

[Hurler Syndrome](#)

[Hypophosphatasia, Autosomal Recessive](#)

[Inclusion Body Myopathy 2](#)

[Isovaleric Acidemia](#)

[Joubert Syndrome 2](#)

[Krabbe Disease](#)

[Limb-Girdle Muscular Dystrophy Type 2D](#)

[Limb-Girdle Muscular Dystrophy Type 2E](#)

[Lipoamide Dehydrogenase Deficiency](#)

[Long Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency](#)

[Maple Syrup Urine Disease Type 1B](#)

[Medium Chain Acyl-CoA Dehydrogenase Deficiency](#)

[Megalencephalic Leukoencephalopathy With Subcortical Cysts](#)

[Metachromatic Leukodystrophy](#)

[*MTHFR Deficiency](#)

[Mucopolidosis IV](#) **ACMG**

[Muscle-Eye-Brain Disease](#)

[NEB-Related Nemaline Myopathy](#)

[Niemann-Pick Disease Type C](#)

[Niemann-Pick Disease, SMPD1-Associated](#) **ACMG**

[Nimblegen Breakage Syndrome](#)

[Northern Epilepsy](#)

[Pendred Syndrome](#)

[PEX1-Related Zellweger Syndrome Spectrum](#)

[Phenylalanine Hydroxylase Deficiency](#)

[Polyglandular Autoimmune Syndrome Type 1](#)

[Pompe Disease](#)

[PPT1-Related Neuronal Ceroid Lipofuscinosis](#)

[Primary Carnitine Deficiency](#)

[Reagan-Henry Syndrome Type 1](#)

Multiplex Panel Screening

Pro

- Cost effective (if only include direct cost of testing)
- Efficient
- Allows universal screening without regard to ethnicity

Con

- Too many unexpected findings (35% or so)
 - Need to screen the partner in all of these
- Disorders rare, esoteric, complex to explain

Universal Screening

- With advances in genetics, paradigm for testing will have to change from methodical, single disorder approach to broader screening
- Counseling by necessity will be more generic
 - “Do you want testing for birth defects?”
 - “Outcomes vary widely but generally none are desirable.”
 - “Not everything is detected by these tests.”

Final Thoughts

“.....the foremost purpose of prenatal screening is not to reduce the incidence of genetic disease but to fulfill a couple's reproductive goals.”

Rowley, Loader and Kaplan; *Am. J. Hum. Genet.* 63:1160–1174, 1998

Peter T. Rowley, MD
1929–2006

Question:

- If a patient has no family history of cystic fibrosis, the chance that she will be found to be a carrier of the disorder is:
 1. Extremely low
 2. Dependent upon her racial and ethnic background
 3. Dependent upon her age
 4. Much higher if she has an expanded panel of more mutations tested

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