Prenatal Genetic Carrier Screening

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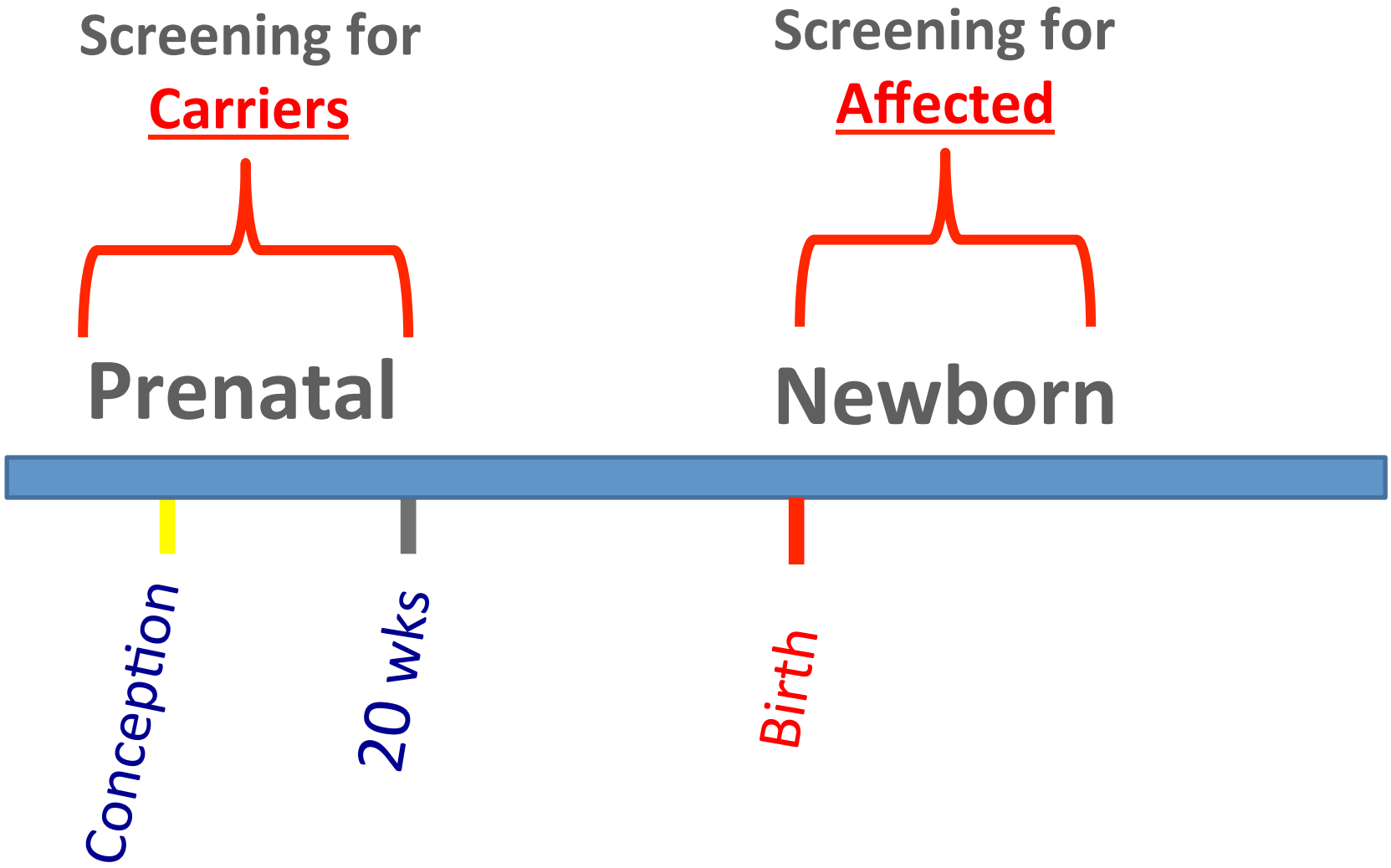
Prenatal Carrier Screening

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



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

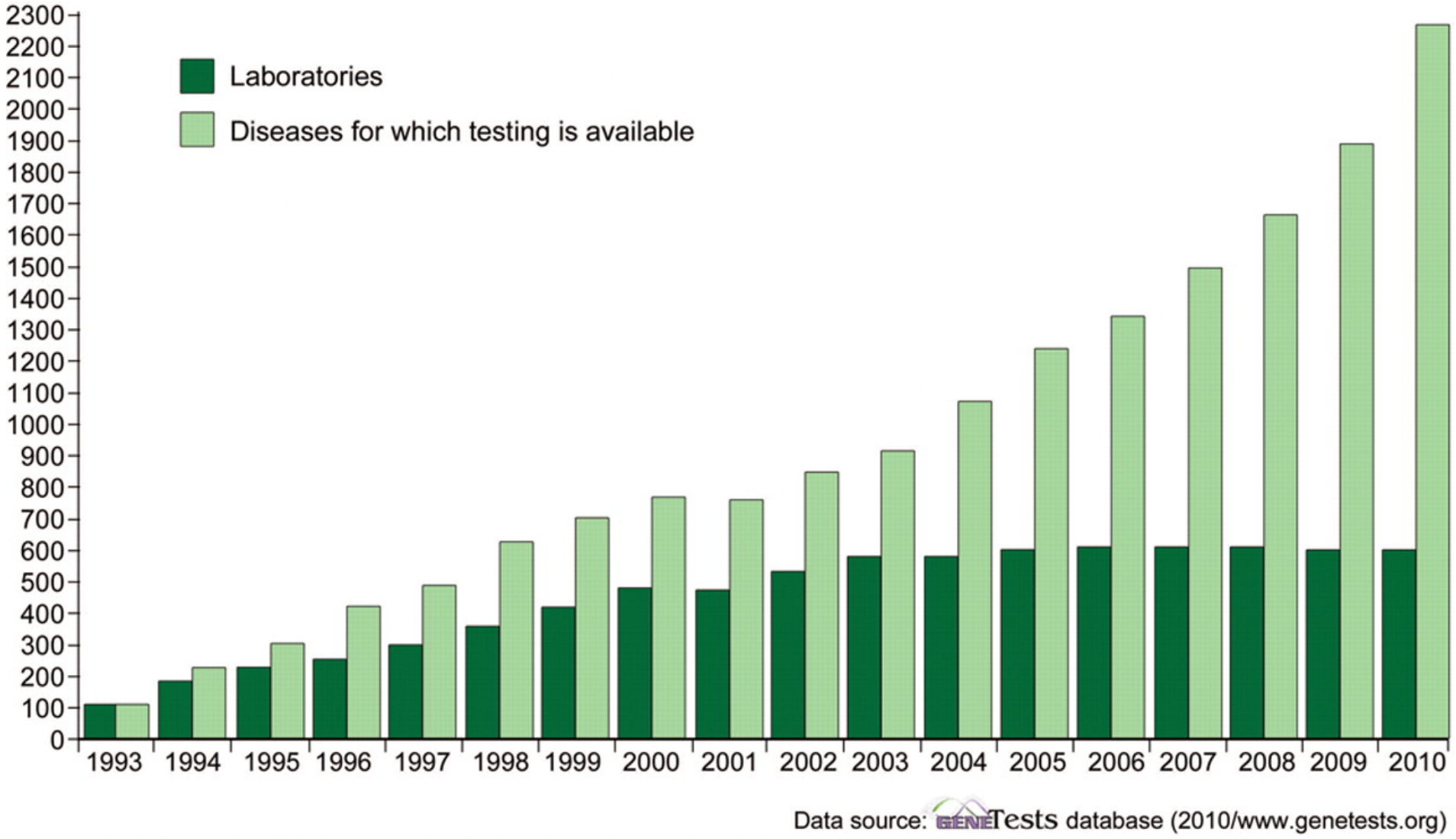
Genetic Diseases are Not as Rare as we Think!

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



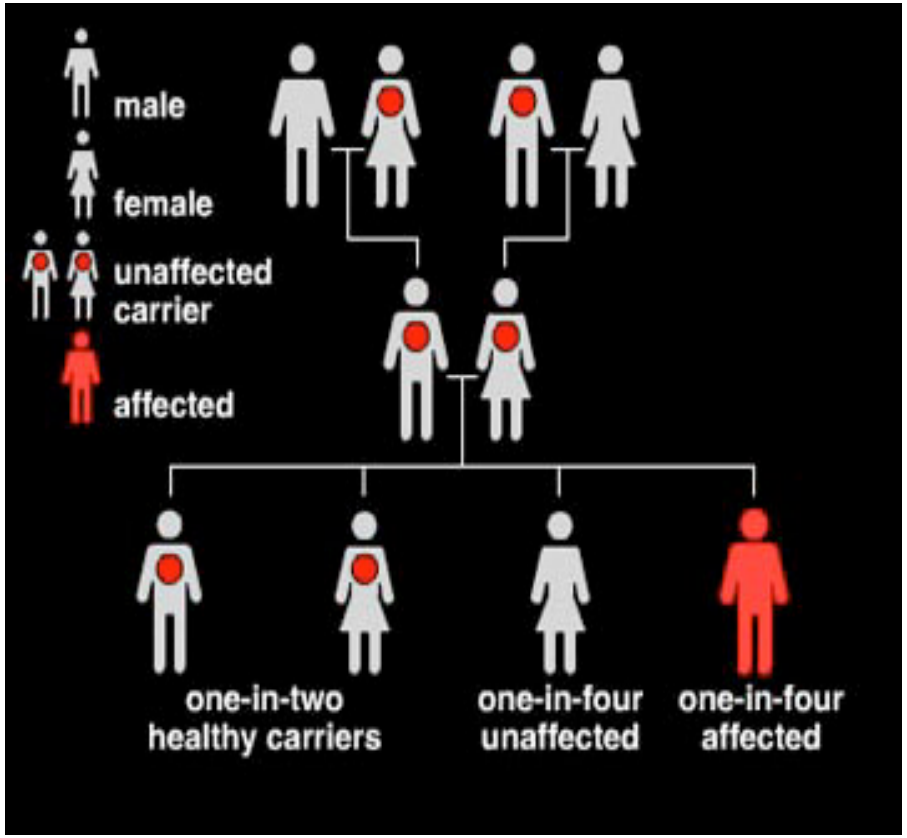
Carrier screening

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

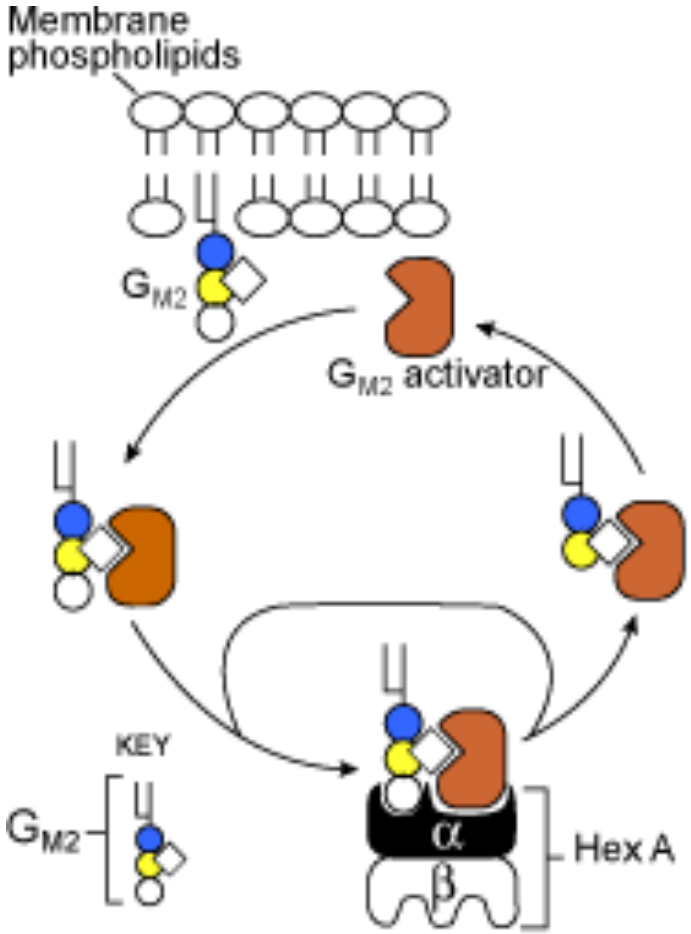
Ethnicity Based Screening

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

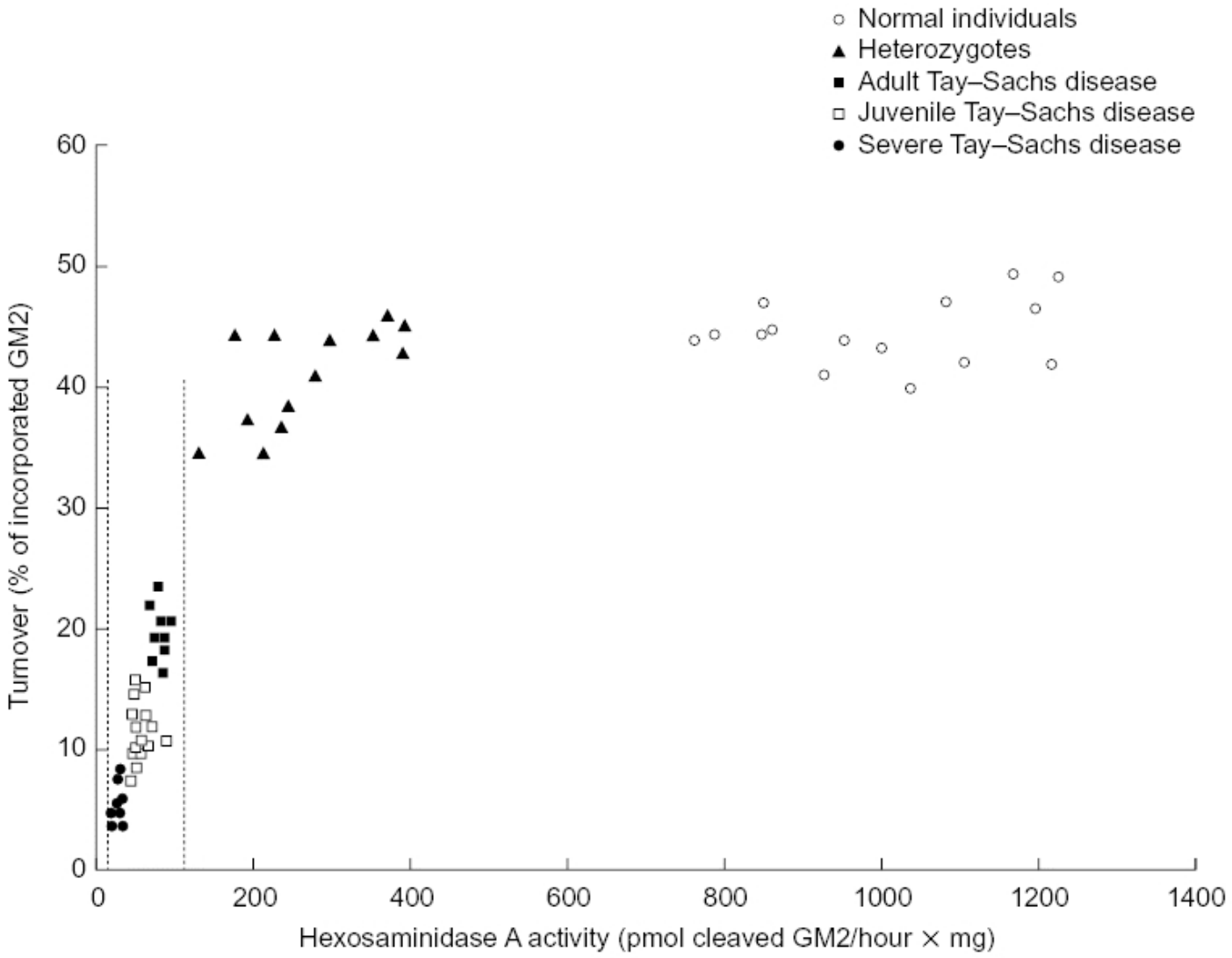
- May present barriers by requiring knowledge of who to screen for which disorders
- Perpetuates categorizing of patients by race and ethnicity
  - Can be seen as stigmatizing
- Less robust with increasing multiculturalism
  - Less clear how to assign patients to a single ethnic or racial group in modern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



UCSF

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

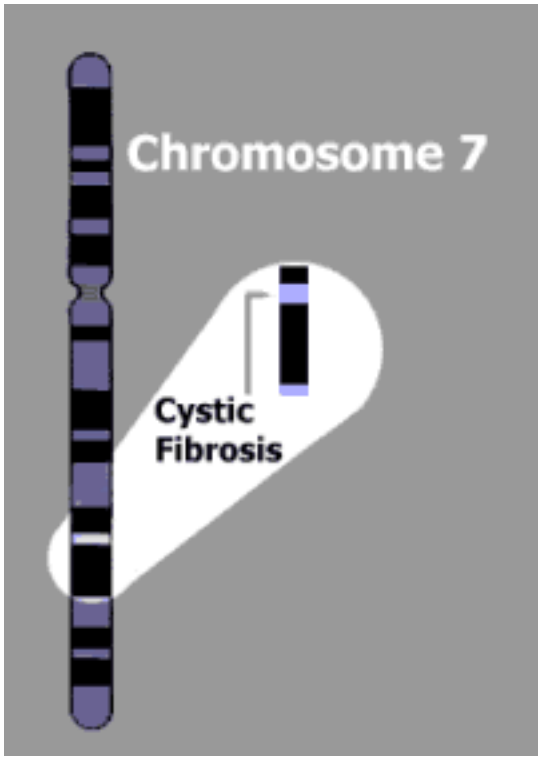
Enzyme assay vs DNA?

- 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*

Group	Carrier risk	Detection rate	Carrier risk w/neg test
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

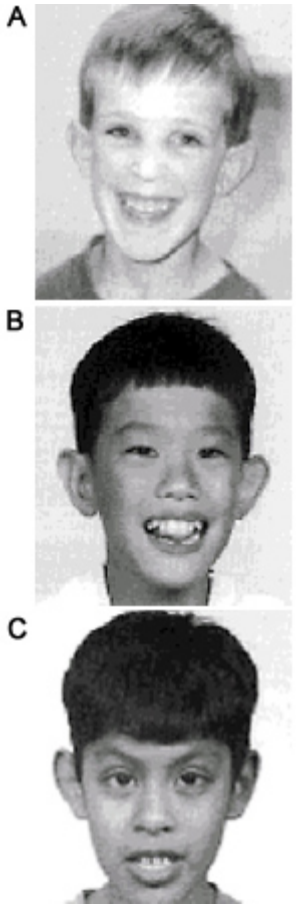
CF mutation analysis

- 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!

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

Fragile X Syndrome



- 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

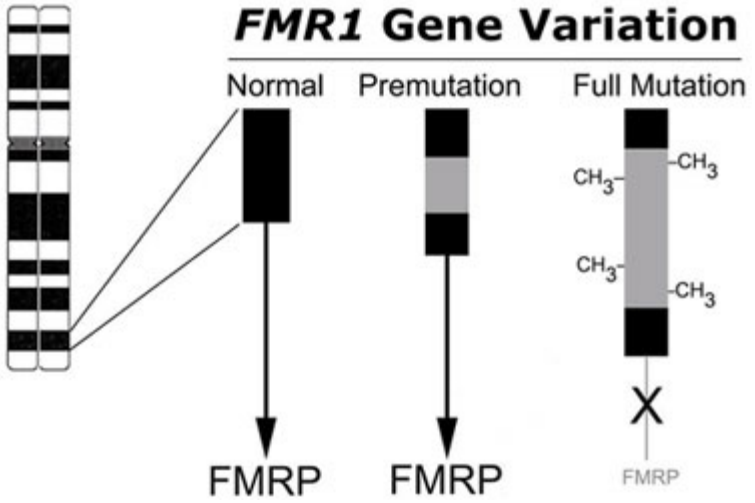
Fragile X Syndrome: Other features

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
Citrullinemia 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
Fanconi Anemia Type C 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
Mucolipidosis IV ACMG
Muscle-Eye-Brain Disease
NEB-Related Nemaline Myopathy
Niemann-Pick Disease Type C
Niemann-Pick Disease, SMPD1-Associated ACMG
Nijmegen 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
Primary Hyperoxaluria 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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