An Overview of Issues Facing Carrier Screening in Large Populations

Presented at an NIH-Sponsored meeting:
"Population-Based Carrier Screening for Single Gene Disorders: Lessons Learned and New Opportunities"
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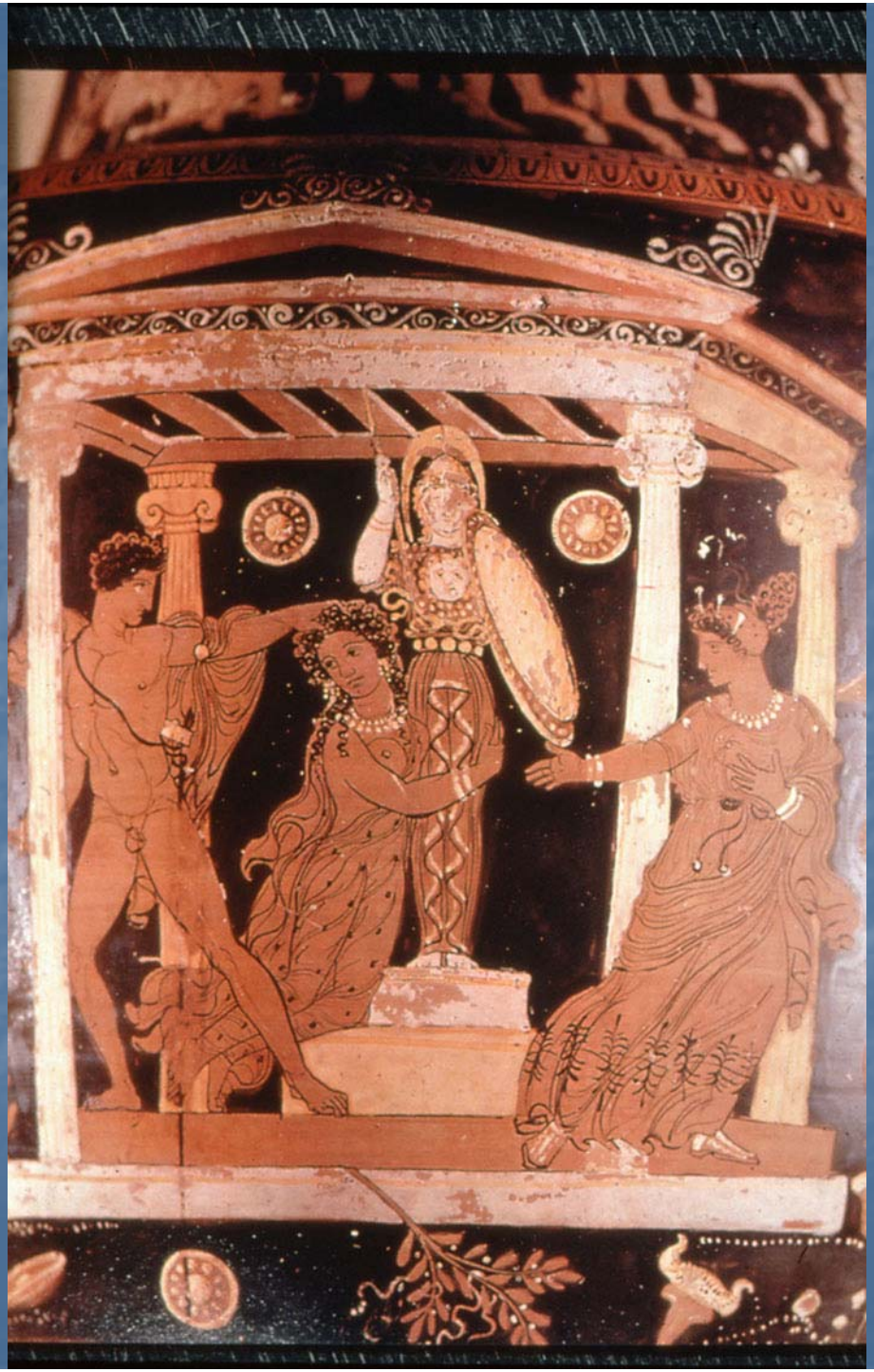
By
Louis J. Elsas MD
Professor and *emeritus* Director
The Dr. John T. Macdonald Foundation
Center for Medical Genetics
University of Miami
Miami, Florida

Issues (Ethical, Economic and Technical) from Carrier Screening for:

- Tay Sachs Disease
- Cystic Fibrosis
- Sickle Cell Disease
- Spinomuscular Atrophy (SMA)
- Fragile X Premutation



The Cassandra Myth: Prediction as a Tragic Curse

Putative Ethical Principles Relevant to Carrier Testing

1. Beneficence
   - The primary benefit is to give reproductive risk information and alternatives to high risk couples.
2. Non-Malfeasance
   - Anxiety, discrimination, expense, stigmatization
   - Cultural sensitivity
3. Autonomy
   - Respect for the individual's rights
   - Informed consent
   - Voluntariness
4. Justice
   - All individuals are treated fairly and equally

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 and cost effective to all.
4. IVF, prenatal diagnosis and termination are options.
5. Consent (informed and voluntary participation) is protected.
6. Knowledge of benefit and harms for carrier testing is transmitted to the screenee pre and post test. Anxiety over probabilistic results is minimized.
7. Privacy is protected (non- discrimination for insurance and job).
8. Stigmatization of the carrier by the community is minimized.
9. Experienced professional resources are required.

UMMG Reimbursement for Carrier Testing

	List Price $	Medicare $	Medicaid $	Private Insurance $	Materials Cost $
FRAX1	272.00	81.46	30.57	96.73	77.60
CFTR(70)	5,982.00	1,719.84	48.96	2,142.39	75.00
CFTR(43)	3,522.00	1,017.24	48.96	1,441.45	55.00
Ashkenazi Panel	1,104.00	439.86	65.46	402.59	135.25
SMA	285.00	87.06	61.85	----------	13.20
S/S (DNA)	229.00	74.84	16.67	----------	24.90
S/S Screen	20.00	7.71	4.00	----------	1.05

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Carrier Screening for Tay Sachs Disease among Ashkenazim Worldwide (ca 1971-1998)

- Total Screened 1,400,000
- Couples at Risk 1,400
- Pregnancies Monitored 3,200
- Pregnancies Terminated 600
- Babies Saved 2,600

Kaback M. Euro. J. Pediatr. 3sup:192, 2000

Tay Sachs Disease Carrier Screening among Ashkenazim: Some Reasons for Success

1. Educated, motivated and accepting community for screening.
2. Pilot study developed data for allele and pseudoallele frequency, and demonstrated disease prevention.
3. Funding from federal and philanthropic sources for pilot studies were followed by professional recommendations for expanding screening for additional diseases (Genet.Med.2008;10:54-56).
4. Fast throughput, valid, and economical methods developed that included both functional (HexA) and specific mutations.
5. Caution for expanding to additional ethnic groups: “admixture”, residual risks and continued need for functional as well as DNA-based screening tests.

Carrier Testing for Diseases More Frequent among Ashkenazim	Residual Risk	
	A Priori Risk	Tested Negative
Tay-Sachs disease (detection rate of **91%)**	**1 in 36**	**1 in 2,800**
Canavan disease (detection rate of **99%)**	**1 in 65**	**1 in 1,540**
Familial dysautonomia (detection rate of **99%)**	**1 in 42**	**1 in 5,000**
Gaucher disease (detection rate of **94%)**	**1 in 19**	**1 in 313**
Fanconi anemia group C (detection rate of **99%)**	**1 in 108**	**1 in 10,753**
Niemann-Pick disease (detection rate of **98%)**	**1 in 125**	**1 in 6,250**
Bloom syndrome (detection rate of **97%)**	**1 in 164**	**1 in 5,556**
Mucolipidosis type IV (detection rate of **95%)**	**1 in 182**	**1 in 3,704**

Technical standards and guidelines for reproductive screening in the Ashkenazi Jewish population, Genetics in Medicine, Vol 10:57-72, Jan. 2008

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Cystic Fibrosis: Another Success Story from Pilot Research Studies of DNA-Based Carrier Detection

1) Began as a funded national consensus study (ACMG/ACOG/NHGRI, 1999-2001). Patient and provider education, test validation.

2) Determined allele frequency among different ethnic groups.

3) Determined acceptance for carrier screening from pregnant couples and pregnancy planners.

4) Differentiated “mutations” from polymorphisms in affected children.

CFTR Mutation Detection Rate	White	Hispanic American	African American	Asian American	Ashkenazi Jewish
ACMG/ACOG 25 mutations*	88.40	71.90	64.51	48.93	94.14
CF39+5**	89.75	73.45	68.61	54.53	94.14
CF 70+6**	91.22	81.03	77.54	54.53	94.14

***Genet Med. 2004 Sep-Oct;6(5):387-91**
****Genet Med. 2007 Nov. 9:739-744.**

CFTR Carrier Testing: Residual Risk for Negative Test

Ethnic Group	Carrier Risk A priori (ACMG)	Residual Risk If 39+5 negative	Residual Risk If 70+6 negative
Ashkenazi Jewish	1/29	*1/470*	*1/470*
European Caucasian	1/29	1/280	1/310
Hispanic American	1/46	1/170	1/240
African American	1/65	1/210	1/290
Asian American	1/90	*1/200*	*1/200*

Some Points to Consider for Cystic Fibrosis Carrier Testing

1) Most babies with CF are born to parents who do not know they are carriers*: Parental/professional acceptance for genetic testing has been lower in this group than for prenatal carrier testing.
2) Prenatal DNA testing could detect most carrier couples before they have their first baby with CF.
3) Hypothesis: An international, controlled carrier testing pilot study of parents-to-be would be acceptable and reduce the frequency of CF in newborns.

*Massie J., et al, J. Paed. Child Health, 43:721-723, 2007

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Screening for Carriers of Sickle Cell Disease

Do not repeat mistakes of the past:

Discrimination of the heterozygote; Need for genetic counseling resources for a common mutant allele (S/S=1/400 African Americans and S/A=1/10); Racism issues regarding reproductive genetic counseling; Should carrier screening be implemented through newborn screening (testing parents of an affected child)?; Stigmatization of the carrier; Expense of the test (inexpensive cellulose acetate and isoelectric focusing for NBS, but DNA-based costs are greater if prenatal monitoring is an option?); Validation of methods used.

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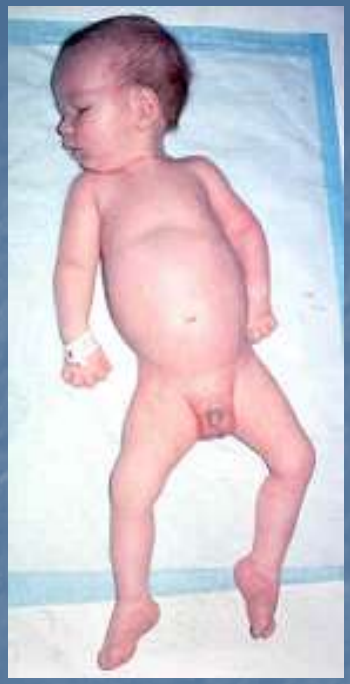
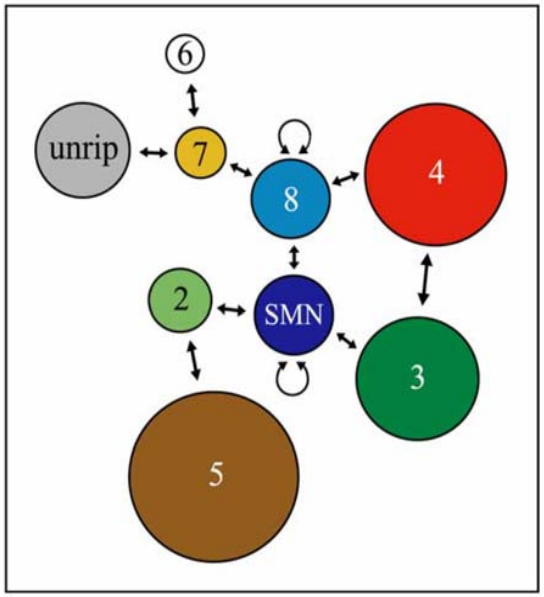
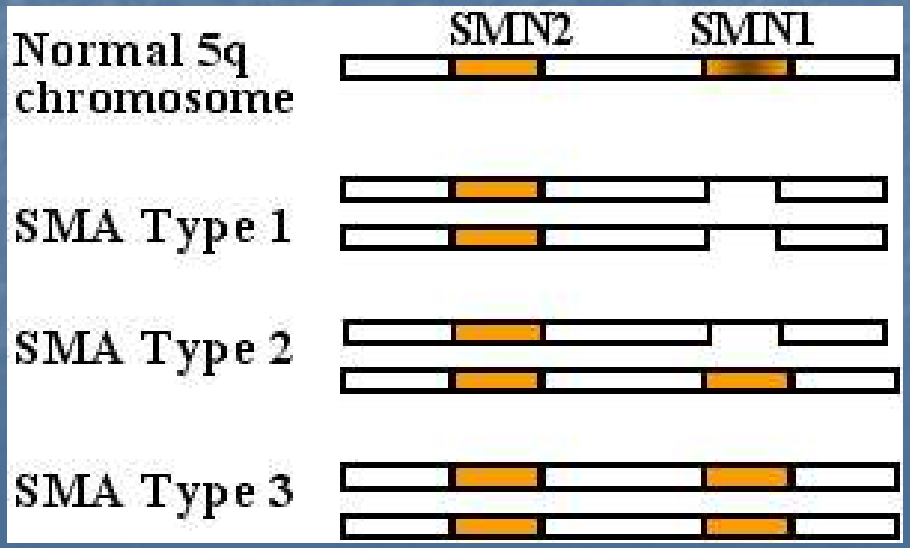
Carrier Screening for SMA 5q



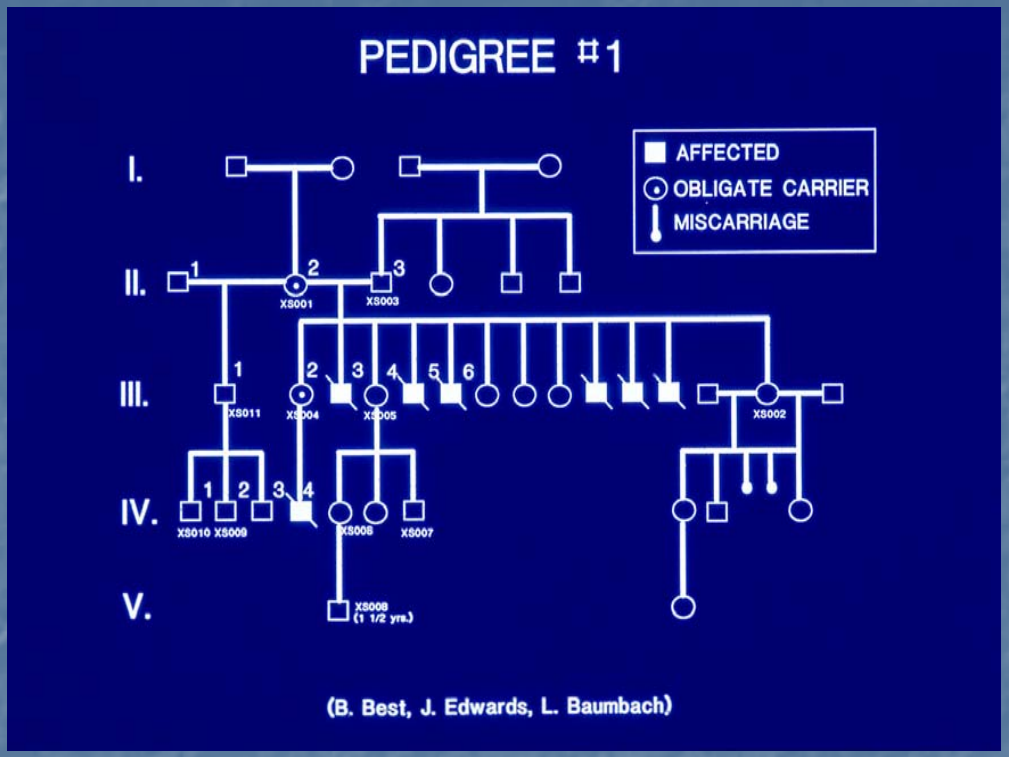
CURRENT CONCEPT OF SMN/GEMIN COMPLEX

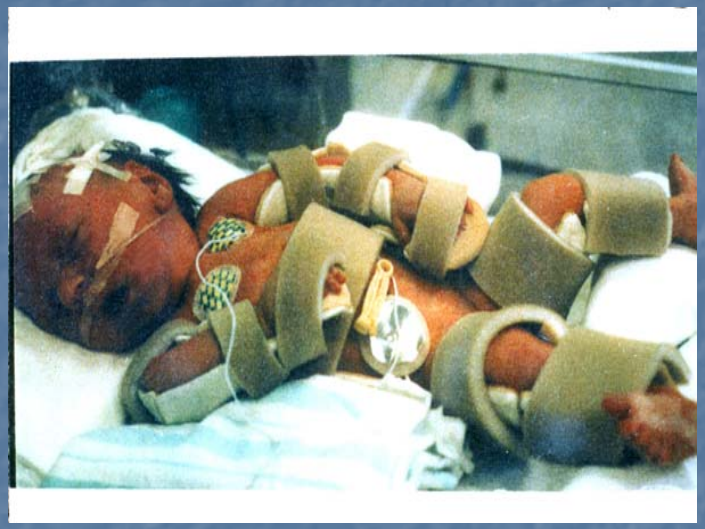


Otter S et al, *J Biol Chem*. (2006) Dec 18



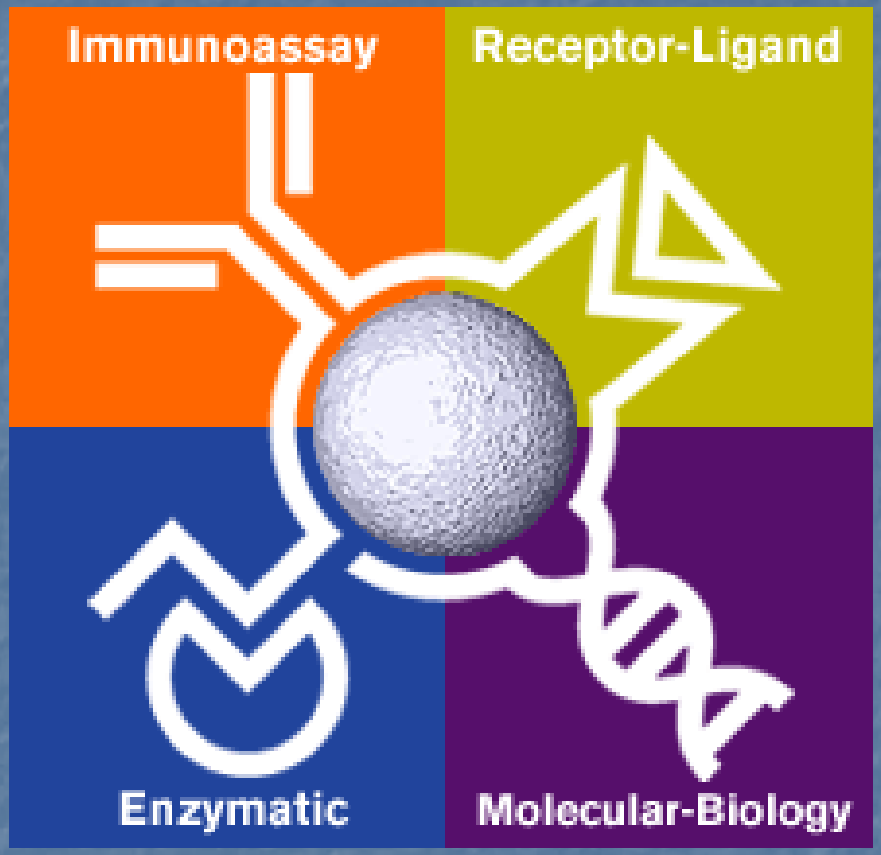
X-Linked Recessive SMA

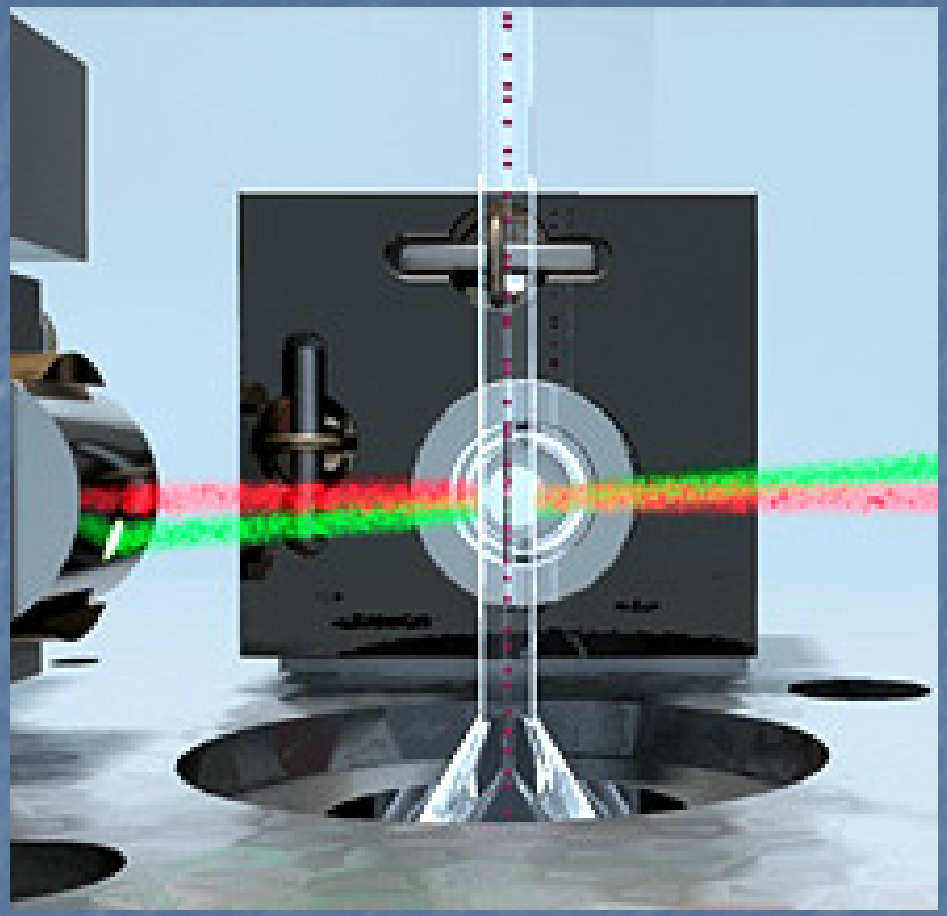




"UBE-1" , Am. J. Hum. Genetics Vol 82, Jan. 2008

Microsphere Technology (Luminex)





SMA carrier testing is a dosage assay for the SMN number ($5/BS); Compare with multiplex PCR and SNP platforms for the CFTR and Jewish disease panels.

Issues (Ethical, Economic and Technical) from Carrier Screening for:

Spinomuscular Atrophy (SMA)

Need federal support for a pilot research studies to:

Determine community acceptance and allele frequency; Diagnose newborns for intervention that might prevent neuronal degeneration; Provide pre- and post-test Genetic counseling ; Determine economics of testing methodology (Dosage of SMN by fragment analysis using Luminex platform only 3 beads @$5/test)

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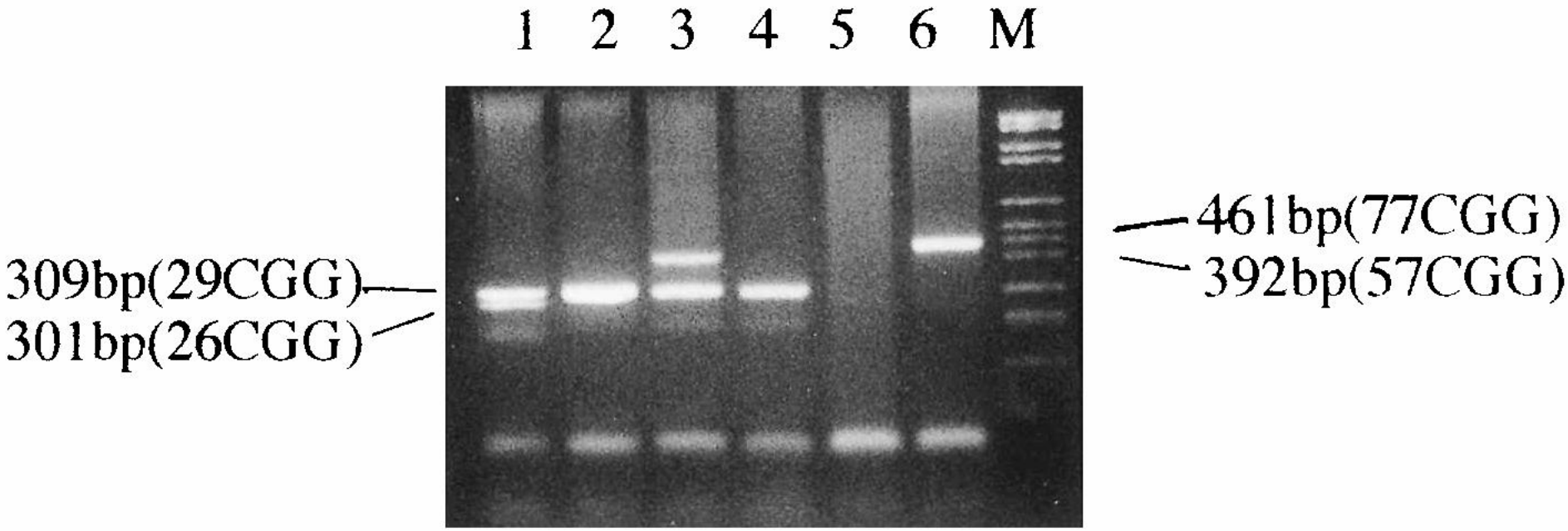
Fragile X Syndrome: Diagnostic and Carrier Testing

- Frequency of phenotype = 1/4,000 males; 1/8,000 females; 1/260 females carry a premutation; panethnic.
- Genotype/Phenotype based on number of –CGG- repeats in 5' FRAXA gene; 6-45="Normal"; 45-55="Gray Zone"; 55-200="Premutation" (ovarian failure, FXTAS ?) ; >200="Full mutation" (almost always associated with MR in males, ? in females)
- Indications for prenatal Fragile X Testing; Family history; Mental retardation, autism, developmental delay (either sex), fetuses of known carrier (premutation) mothers, other clinical suspicion.*

Population Based Carrier Screening was NOT recommended because: Limited knowledge about intermediate expansions; could not predict phenotype in females; both community and physicians lacked knowledge about fragile X; Limited counseling resources; Lack of knowledge about community acceptance; Costs of methods (PCR and Southern blot).*

*ACMG/ACOG Recommendations Ca.1994-2001

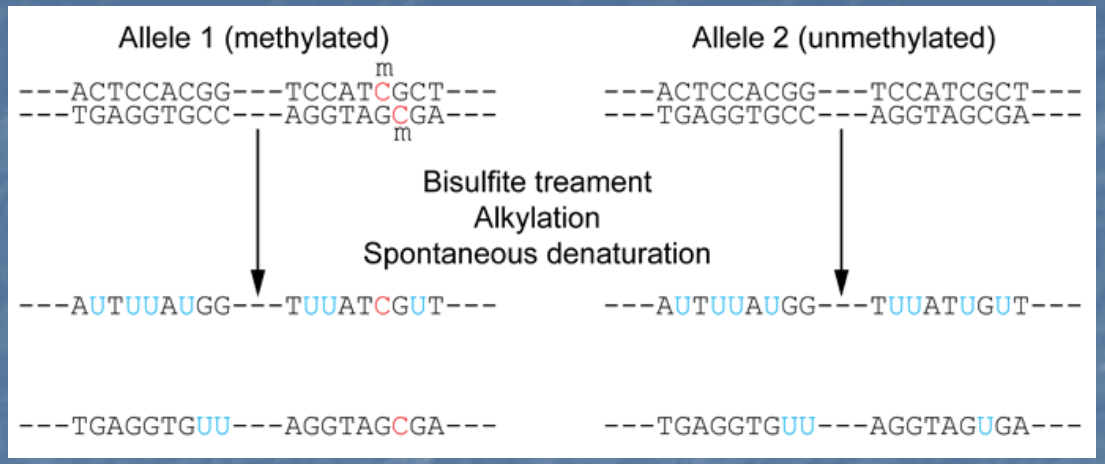
A Strategy for Fragile X Carrier Screening



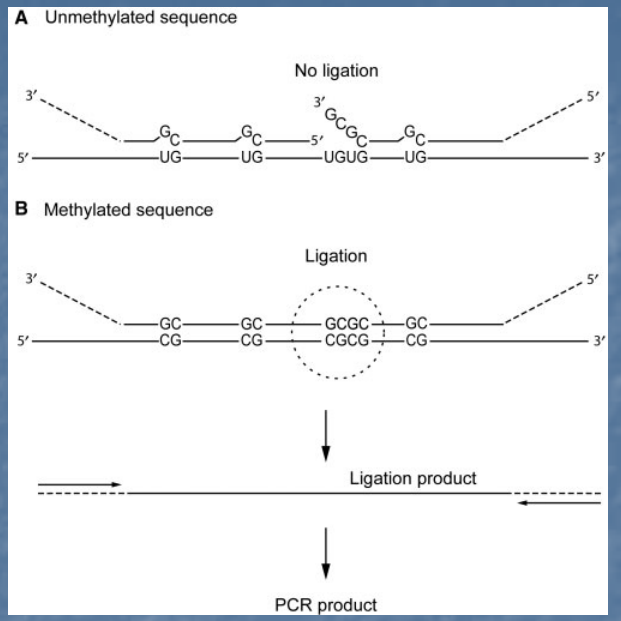
Metaphore Gel electrophoresis of FMR1 PCR Fragments

Melis M., Addis m., et al Genetic Testing3:301-305, 1999

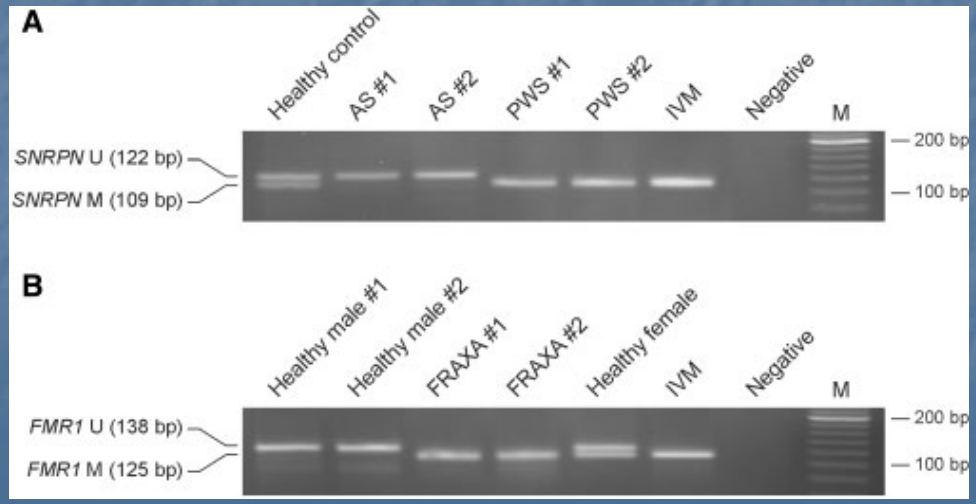
Fragile X Newborn Screening ??(Conceptual)



Bisulfite treated DNA



Ligation with methylation specific probes



Aberrant Methylation of FMR1 Promoter

Dahl C and Guldberg P, Nucleic Acids Research, 2007, Vol. 35, No. 21

"Here's my sequence..." *The New Yorker*

Direct to consumer DNA Testing

The DNA Age: Direct to Consumer

A) 23andMe (www.23andme.com)

Cost $999; 580,000 SNPs

B) deCode Genetics (www.decodeme.com)

Cost $985; 1,000,000 SNPs

C) Navigenics (www.navigenics.com)

Cost $2,500; 1,000,000 SNPs

Caveat; "not designed to diagnose disease or medical conditions"

Hunter D, Khoury M, Drazen J, New Eng J Med, 358:105, 2008

Summary of Points to Consider

1. **Is parental knowledge of increased risk for having an offspring with a serious heritable disorder, a necessary/sufficient benefit for public health carrier screening?**
2. **Heterozygote testing produces probabilistic results with residual risks when a screening test is negative for both the screenee and the physician (Wrongful birth). Do we have allele frequency data by ethnicity?**
3. **Is the community educated and accepting of the benefits and harms of carrier testing?**
4. **Do we have the professional resources to provide genetic counseling?**
5. **Do we have phenotypic knowledge and interventional resources for the at risk couples?**
6. **Is there technical and clinical validation of the test?**
7. **What is the Cost/benefit ratio of mass screening?**
8. **There are needs for pilot studies to: Validate methodology (technical and clinical); Determine allele frequency, genotype/phenotype outcome, public acceptance, benefits and harms.**

Thank You

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