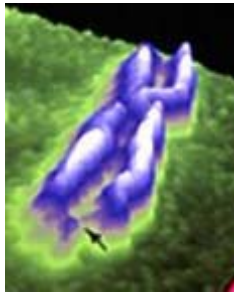
Fragile X Syndrome: Carrier Screening in the Prenatal Population



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Fragile X Syndrome

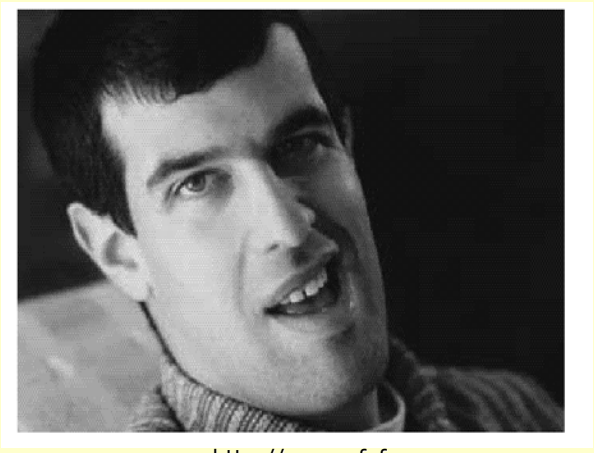
- Why screen for fragile X carriers?
- Who do we screen?
  - Current recommendations
  - Problems
- Population-based screening?
  - Rationale
  - Cost-effectiveness
  - Challenges

Fragile X Syndrome

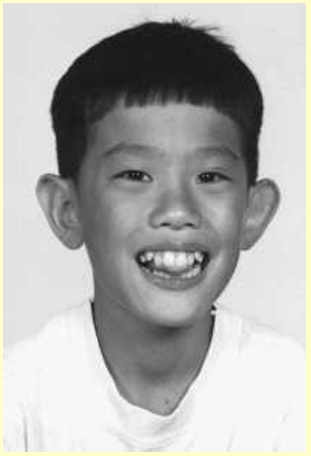
- The most common cause of inherited mental retardation (MR).
- Second only to Down syndrome as an etiology for MR.
- Incidence of approximately 1 in 4000 males and 1 in 8000 females
- Found among all ethnic groups and occurs in families with no history of mental retardation
- 1 in 259 women are carriers of the fragile X premutation
  - Only the mother has to be a carrier for the fetus to be at risk for fragile X syndrome

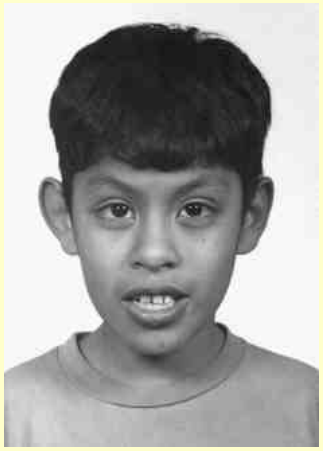
Fragile X Syndrome

- Males:
  - Moderate to severe mental retardation, learning disabilities
  - Long face, prominent ears, macro-orchidism
  - Physical phenotype can be subtle, especially in young boys
  - Hyperactivity, autism (approx. 1/3), hand flapping, hand biting, disordered speech and language
  - males are generally unable to live independently



http://www.nfxf.org

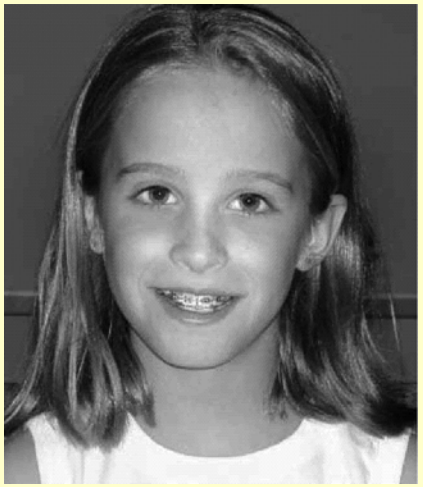




medgen.genetics.utah.edu

Fragile X Syndrome

- **Females:**
  - Less frequent and less severe in females
  - Mild to moderate mental retardation, learning disabilities
    - About 1/3 of females have significant intellectual disability.
  - Long face, prominent ears (more subtle in females than in males)
  - Poor eye contact, attention problems, shyness and social anxiety

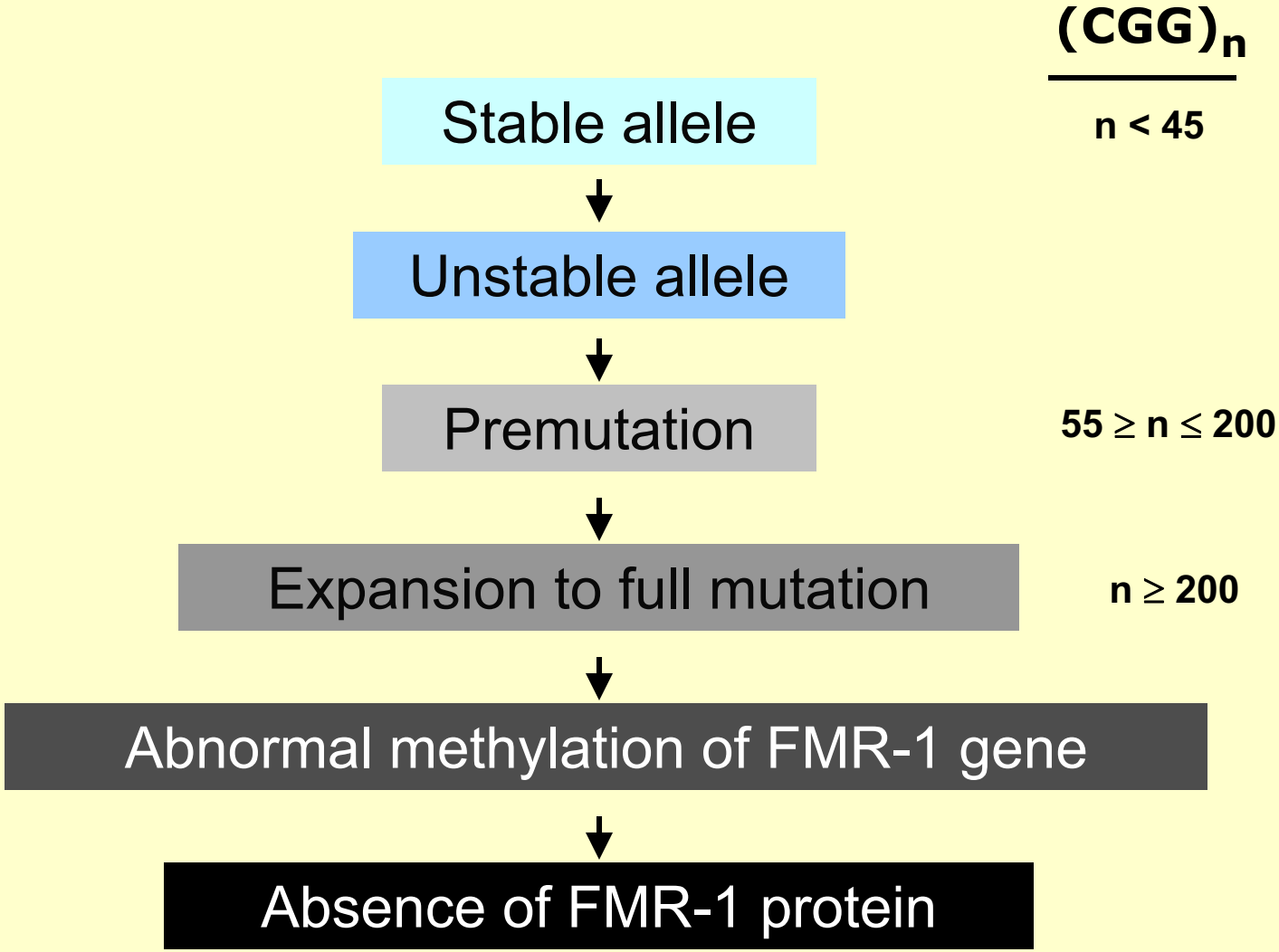


http://www.nfxf.org

A Spectrum of Clinical Involvement

Three Generations: The young man and woman on the right both carry the full mutation for fragile X syndrome. Their grandfather is now affected by FXTAS and is the fragile X syndrome carrier who passed on the carrier status to his daughter, their mother.

FMR-1 gene: a triplet repeat disease



Risk of Premutation Expansion: size of repeat and gender

Maternal Repeat Size	% Of Offspring With a Full Mutation
55-59	3.7%
60-69	5.3%
70-79	31.1%
80-89	57.8%
90-99	80.1%
>100	94-100%

Source: Nolin et al., 2003

A Case for Prenatal Population-Based Carrier Screening?

ACOG / ACMG Recommendations: Fragile X Testing

- **Carrier Testing: only individuals with:**
  - **a family history of fragile X or**
  - **undiagnosed mental retardation,**
  - **developmental delay or**
  - **autism**
- **Prenatal diagnosis: when the mother is a known carrier of fragile X (premutation or full mutation).**

NSGC: www.springerlink.com/media/c5v8ykryqj2rld6ugxuq/contributions/r/5/4/3/r54356r13r0740u7.pdf
ACMG: www.acmg.net/resources/policies/FragileX_GIM_2005.pdf
ACOG: http://www.acog.org/publications/pdfs/co338.pdf

Problems with Current Recommendations

- Risk factor based on screening alone: not effective in detecting carriers.
  - For example:
    - Maximal rate of detection of female PM carriers by active cascade screening (6%) is much lower than that by prenatal screening (60%). (Song et al, 2003).
- Largest proportion of fragile X syndrome births are in families without index cases.

Fragile X carrier screening: rationale

- 1 in 259 women in the general population is a carrier.
  - Higher frequency reported in some studies (Israel).
- Carrier status is essentially silent in reproductive years.
  - except possible ovarian dysfunction
- Most women with premutations have no knowledge of their potential risk for delivering an affected child.
  - family history does not meet current criteria for screening.
- Most women have no knowledge of their potential risk for premature ovarian failure.

FX Carrier Screening: rationale

- **More than 50% of families had more children after they had a fragile X child, but before that child was diagnosed. (Bailey et al, 2003).**
  - 222 children , 50% of these children had a full mutation
- **Choice: couple can fulfill reproductive goals**
  - The chance to pursue assisted reproductive technology in order to avoid conception of an affected child.
  - To consider termination of a pregnancy, or
  - To prepare for the birth of a chronically ill or special needs child.

Current Practices in Prenatal Screening

- Offer maternal serum screening (includes ultrasound) to all pregnant women to detect chromosomal abnormalities (eg. **Down syndrome) and open neural tube defects**
- Offer **Cystic Fibrosis** carrier screening to all pregnant or preconception women of Caucasian or Ashkenazi Jewish ethnicity (make available to other ethnicities that have lower carrier frequencies).
- **Hemoglobinopathy** screening: almost universal.
- Targeted screening for diseases prevalent in specific ethnic groups (eg. Canavans, Tay-Sachs, FD).

Current Prenatal Screening: Frequency Comparison

- 1 in 625 couples are carriers for cystic fibrosis
- 1 in 270 risk of aneuploidy at age 35
  - 1 in 750 overall in North America
- 1 in 800 + risk of neural tube defect in gen pop.
- 1 in 259 women are carriers for fragile X.

Does Fragile X meet general principles of carrier screening?

1. The disorder should be considered a significant health problem or carry a burden of disease.
2. Diagnostic testing must be robust.
3. Screening should be accomplished in a simple manner.
4. Screening should be cost-effective.
5. There should be effective treatment or intervention for a positive result.

Wilson & Jungner, 1968; Khoury et al 2003

→ **Are patients interested?**

Screening principles:

1. Significant Health Problem

- Significant morbidity associated with fragile X syndrome.
- Significant cost of raising a child with fragile X syndrome of $615K (estimates range $500 to $1.1 million).

Source: Musci and Caughey, 2005 ; Finucane et al., 1996

Screening principles:

3. Screening Should Be Simple

- Sample collection and patient education could be added to the existing prenatal genetic testing:
  - maternal serum screening: Down Syndrome, NTDs.
  - cystic fibrosis

Screening principles:

4. Is screening cost effective?

- A method for comparing the relative value of various clinical strategies:
  - Cost for a given **health benefit**.
  - How the individual values the health state or outcome.

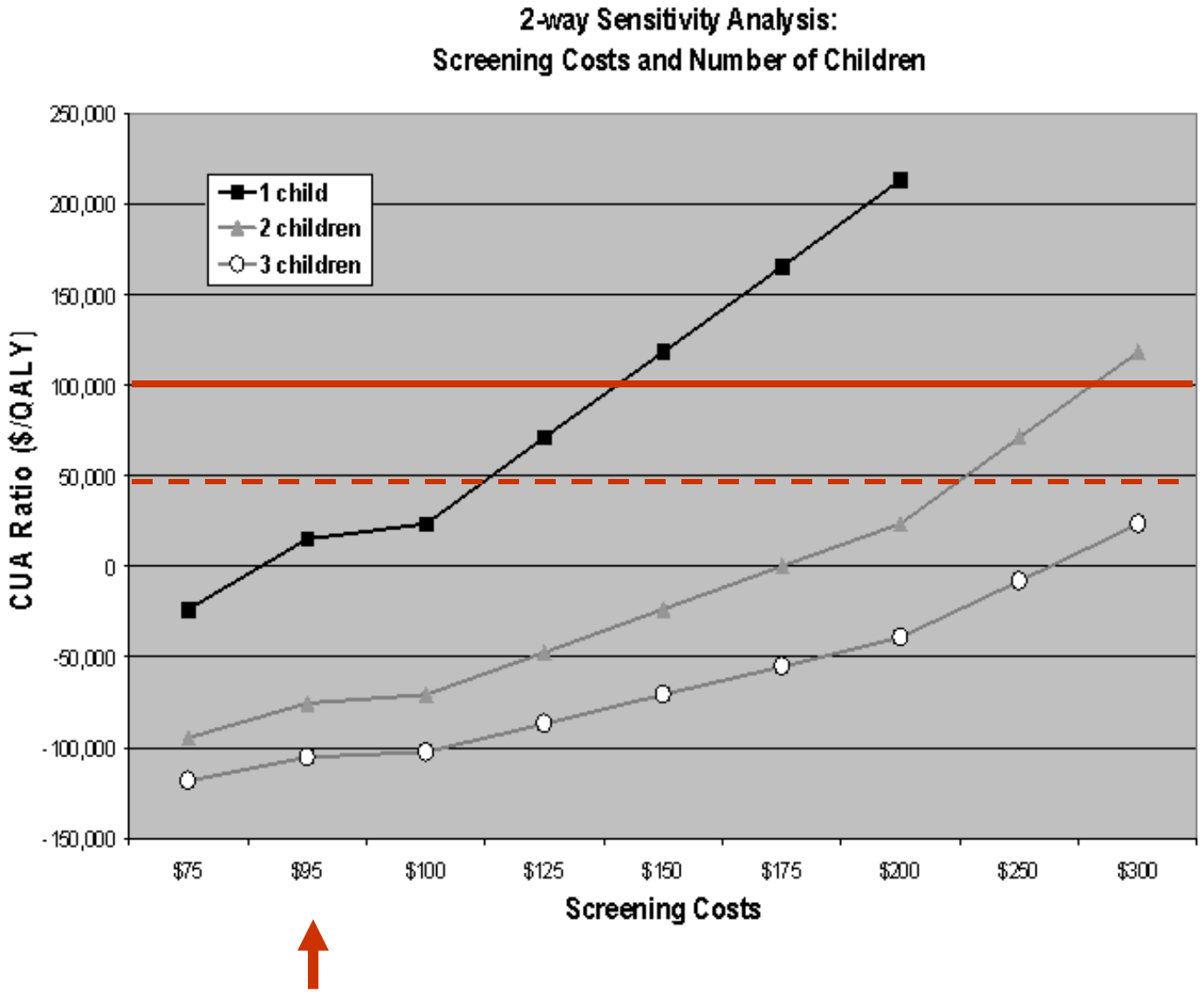
$$\text{cost effective} \neq \text{cost saving}$$

Cost Effectiveness Analysis

- Cost-utility analysis
  - Cost of $549K per fragile X diagnosis
  - Less than the cost of raising a child with this disorder
- Widespread fragile X carrier screening strategy
  - Identify 86% of the approximately 750 fragile X affected fetuses annually
  - **13% of patients who present too late to obtain prenatal diagnosis**
- The program would be cost-effective yielding a **cost-utility ratio** of $14,858 per Quality Adjusted Life Year (QALY).
  - At a cost of $95 per test.
  - One child per patient.

Musci and Caughey, AJOG, 2005

Screening costs vs. number of children



Assumptions for baseline model:

- 80% of women could be screened with PCR alone, the remaining 20% would require Southern blot analysis.
- All women with a positive carrier test would undergo amniocentesis.
- Patient preferences based on published data for Down Syndrome.
- 87% of women with fragile X fetus would undergo pregnancy termination.

Musci and Caughey, AJOG, 2005

Attitudes toward prenatal carrier screening for Fragile X: a pilot study

- Pretest knowledge about Fragile X was limited:
  - 33% had heard of Fragile X syndrome before enrollment.
- Post-counseling: knowledge still limited.
- Participants were strongly in favor of being tested or screened.
- Participants did not experience undue anxiety with screening.
- Respondents hoped that knowledge of Fragile X in the general population would increase.
  - Recommended screening be offered during routine prenatal care.

Fanos, Spangner,and Musci: Genetics in Medicine 2006

Arguments against routine screening:

- The genetics is too complex.
  - Current education and counseling resources inadequate.
  - Genetic “manpower” shortage in United States.
- Cannot predict phenotype for female fetuses with full mutations.
- Lack of data regarding the **preferences, attitudes and informational needs** of patients.
- Burden on primary care obstetrician to provide informed consent: Time, effort, liability(?).
- Cost

Arguments for routine screening:

- Meets screening criteria: high incidence; associated with significant morbidity; a reliable test, cost-effective.
- Women who screen negative during one pregnancy do not need to be tested again in subsequent pregnancies.
- Women concerned about chromosome abnormalities, including Down syndrome, are interested in testing for other common causes of mental retardation.
- Systems for prenatal screening already in place.
- Only the mother needs to be offered carrier screening

Challenges :

- To **reduce the cost** of DNA assay:
  - PCR : screening v. diagnostic testing
    - 10+ % would require Southern to resolve
    - Diagnostic testing for positives
  - High-throughput : sample number & rapid ‘turnaround’
- Obtain data regarding the **preferences, attitudes and informational needs** of patients for FX screening
  - Delivery of information & counseling
- Education of primary care physicians

To be done:

- Prospective study of fragile X screening program in order to:
  - better **understand patient attitudes, preferences, and behaviors**.
  - **Determine best DNA test and logistics.**

END

A Spectrum of Clinical Involvement

Three Generations: The young man and woman on the right both carry the full mutation for fragile X syndrome. Their grandfather is now affected by FXTAS and is the fragile X syndrome carrier who passed on the carrier status to his daughter, their mother.

Fragile X Associated Conditions Among <u>Carriers:</u>

- Premature ovarian failure (POF)
  - 20 % of premutation carriers have POF vs 1% in general population
  - Premutation alleles were found in 14% of women with a family history of POF and no known history of fragile X syndrome
- Fragile X Associated Tremor and Ataxia (FXTAS)
  - Neurological condition in some male adult carriers of the FMR1 premutation.
    - First described by Hagerman et al in 2001.
  - 30 - 40% of men 50+ years old with a premutation have FXTAS
    - estimated 13-fold increased risk of these symptoms compared with non-carriers
  - Has been reported in female premutation carriers (also >50 y.o.), though symptoms milder.
    - (Hagerman, et al. 2004; Berry-Kravis, et al. 2005).

Molecular Basis: FMR-1 gene

- The fragile X mutation is an unstable CGG repeat that can expand dramatically (to a full mutation) when passed from mother to offspring
- Full mutation alleles are associated with abnormal methylation, which turns off FMR-1 protein production
- Loss of FMR-1 protein function interferes with normal brain development
- FMR-1 protein is absent in full mutation males

Fragile X Inheritance

- Both males and females can pass the mutation on the X chromosome
  - Women to either their sons or daughters and men to all their daughters but none of their sons
- Expansion of the CGG repeat is influenced by
  - <u>The gender of the carrier:</u>
    - Premutation females are at risk to have full mutation offspring while the premutation in males remains relatively stable when passed to daughters
  - <u>The number of repeats:</u>
    - In general, larger-sized repeats, in females, have a greater risk to expand to a full mutation in one generation. Alleles are less likely to expand when passed from males.

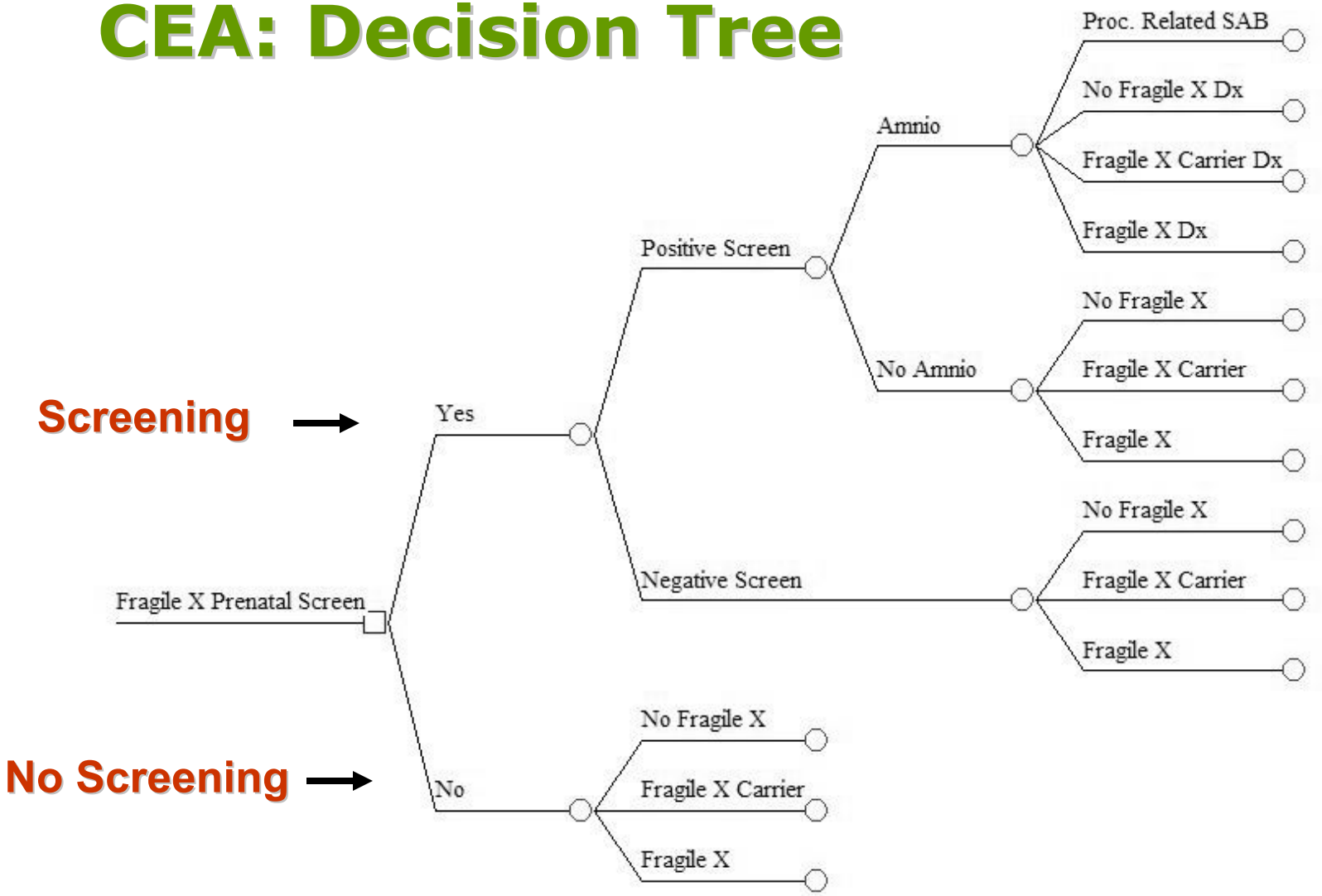
- “…..the foremost purpose of prenatal screening is not to reduce the incidence of genetic disease but to fulfill a couple’s reproductive goals.”

Rowley et al; *Am. J. Hum. Genet. 63:1160–1174, 1998*

Prenatal Screening/Testing:

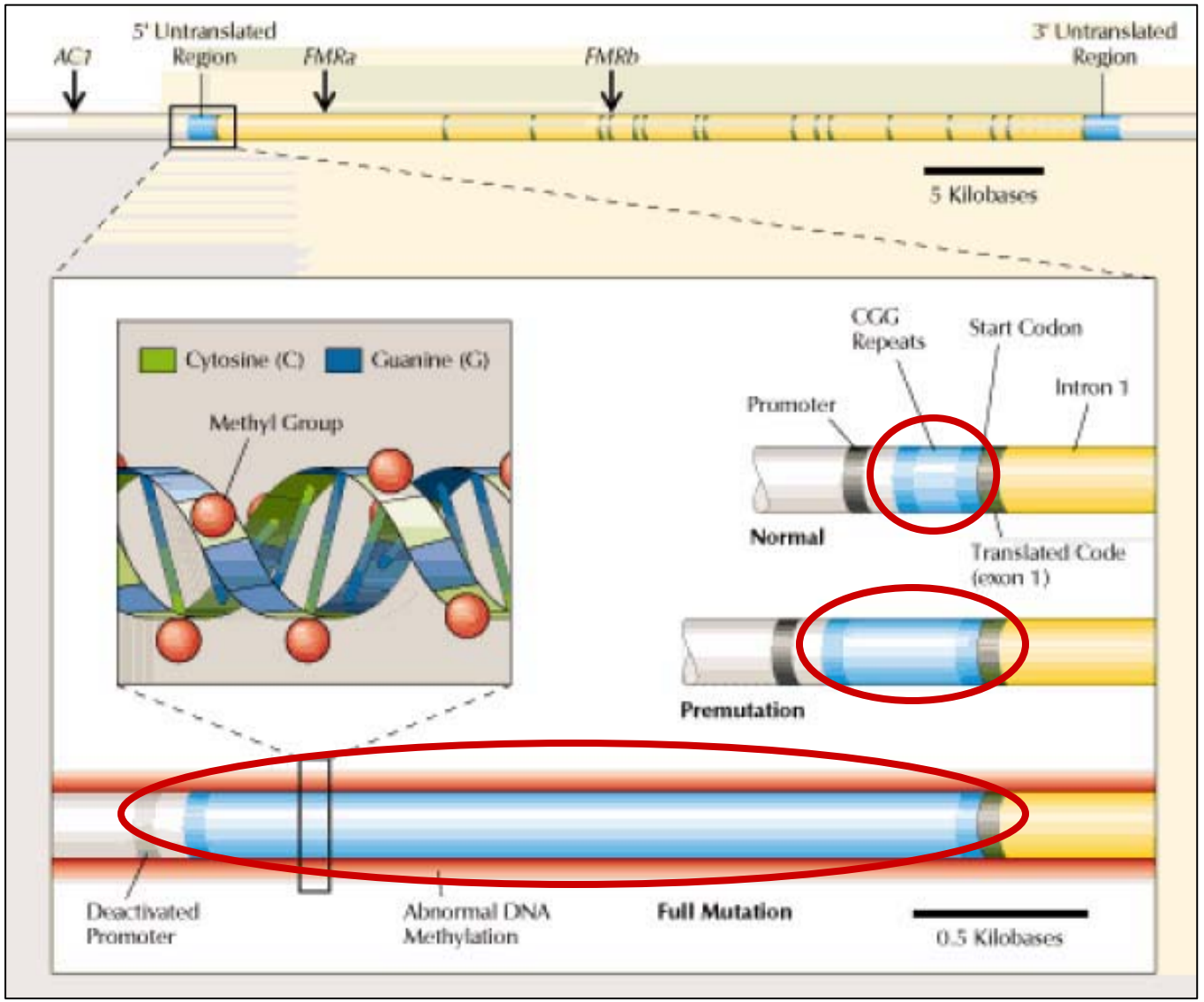
- Provides individuals with
  - The chance to pursue assisted reproductive technology in order to avoid conception of an affected child.
  - To consider termination of a pregnancy, or
  - To prepare for the birth of a chronically ill or special needs child.

CEA: Decision Tree



Musci and Caughey, AJOG, 2005

FMR1: triplet repeat expansion



$(CGG)_n$

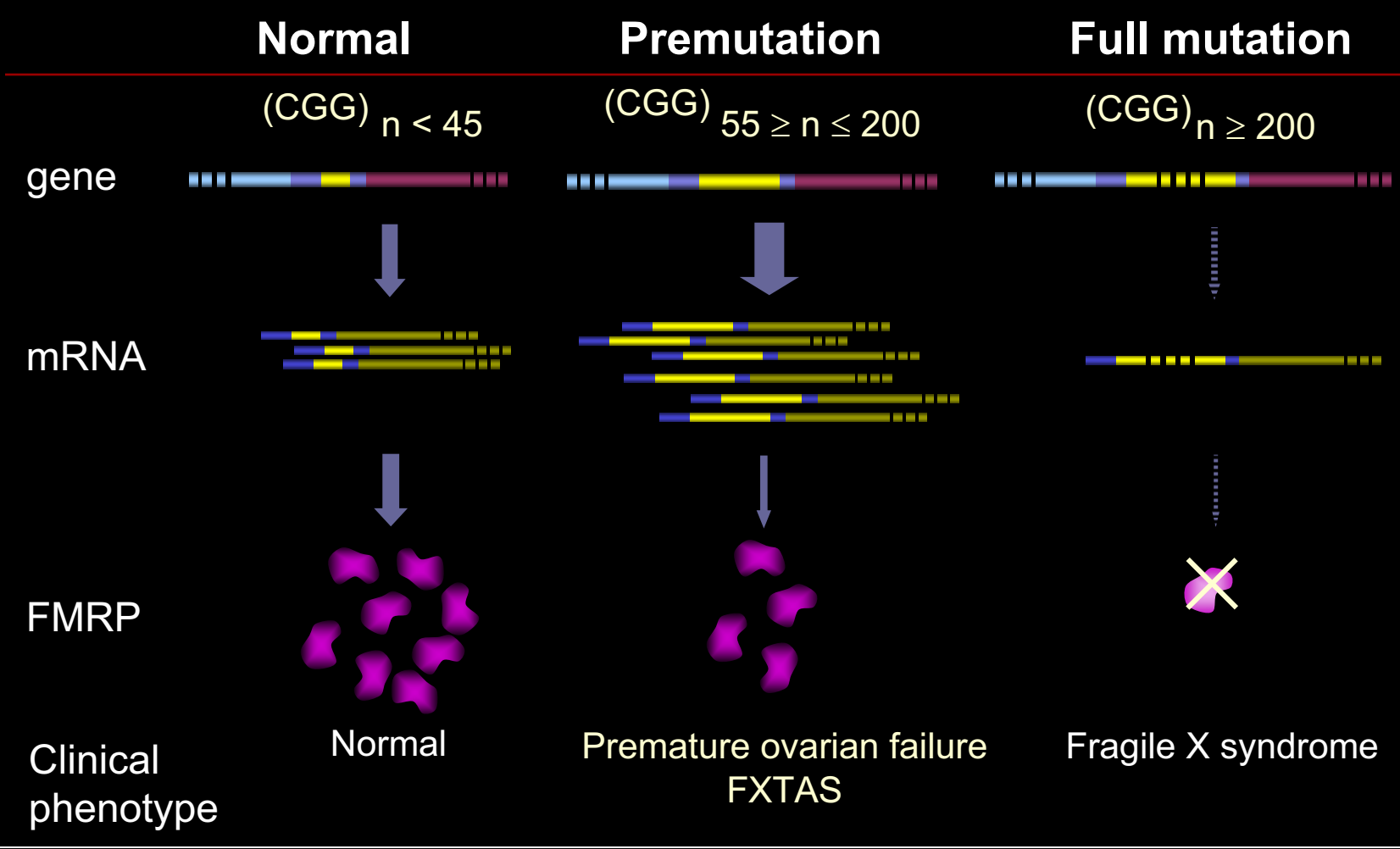
$n < 45$

$55 \geq n \leq 200$

$n \geq 200$

No Transcription = No FMR Protein

The *FMR1* Gene: CGG repeat expansion



Slide: courtesy of Randi Hagerman