

Clinical Genetics I Objectives

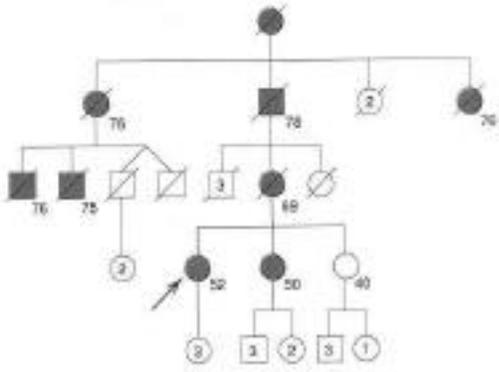
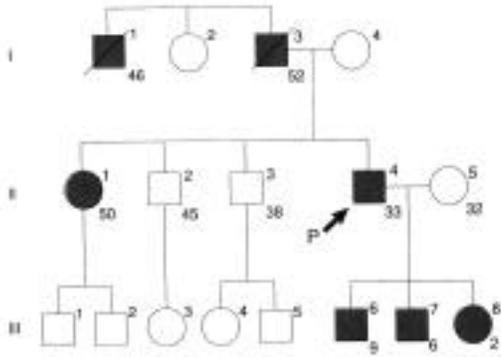
Lecture 23

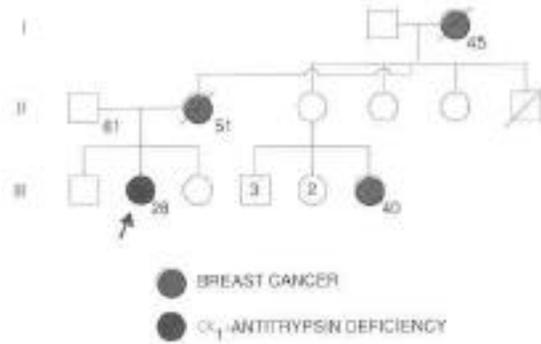
- Know HOW to take a **family history**, and WHY
- Know what **genetic counseling** is, and what the indications for genetic counseling are
- Know how to apply **Bayes' theorem** to problems in clinical genetics

FAMILY HISTORY—WHY should you take one ?

- Diagnosis
- Prognosis
- Prevention and Avoidance of genetic disease

Familial Hypercholesterolemia

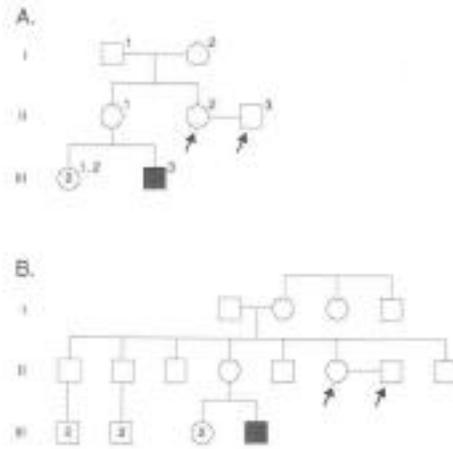




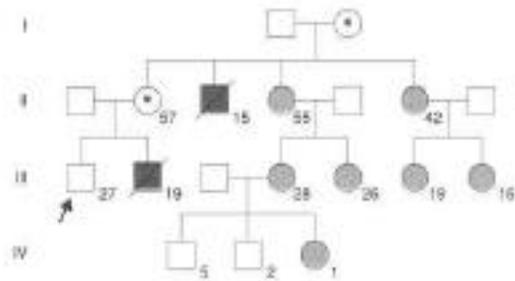
Taking the Family History

- Make it **relevant** to the “Present Illness”
- Ask about early-onset, preventable illness
- Ask specifically about 1st degree relatives
- Ask about informative relatives
- Record ethnic or ancestral background where relevant
- Inquire about consanguinity
- Keep it up-to-date

The importance of relevant negative information



Obligations for relatives



Genetic Counseling

- Genetic counseling is a process of communication that deals with the human problems associated with the occurrence, or the risk of occurrence, of a genetic disorder in a family.
- It is intended to provide such individuals and families with information about their condition, to explore the personal consequences of this information, and to aid families at risk to make informed reproductive decisions.

Goals of genetic counseling are to help individuals and families to

- Comprehend the medical facts including diagnosis, prognosis and management
- Appreciate the way heredity contributes to the disorder and risk of recurrence
- Understand the alternatives for dealing with these risks
- Choose the course of action that seems appropriate for the individual or family being counseled
- Make the best possible adjustment to the condition or the risk of its recurrence

Table 12.2. Indications for Genetic Counseling

1. Known or suspected hereditary disease in a patient or family.
2. Birth defects.
3. Mental retardation.
4. Advanced maternal age.
5. Family history of early onset cancer.
6. Recurrent pregnancy loss.
7. Teratogen exposure.
8. Consanguinity.

Process of genetic counseling

- Nonjudgmental and not directive
- Dealing with guilt, anger, frustration, and anxiety
- Candor and honesty
- Communication and information transfer
- Social and other support services
- Team effort to promote patient autonomy and psychosocial adjustment

Table 12.3. Information Conveyed in Genetic Counseling

1. The **magnitude** of the **risk** of **occurrence** or **recurrence**.
2. The **impact** of the **disease** on the patient and the family.
3. The possibility of **modification** of either the impact or the risk.
4. **Anticipated future developments**.

Brachydactyly



Down syndrome



Medical (and Genetic) Decision Making --Bayes' Theorem--

- Rev. Thomas Bayes 1701-1761
- How should a person update an existing belief when presented with new evidence ?
- How can one factor prior knowledge into a statistical computation ? (Are the hoof beats a horse or a zebra ?)
- Applications:
 - Microsoft's perky paperclip
 - **Genetic counseling/screening**



Early stages of math anxiety

The Far Side by Gary Larson Copyright Universal Press Syndicate

A leading cereal maker introduces a new brand of cereal. Each box will contain a prize, and there are six different prizes. You purchase two boxes of this cereal. What is the probability that you will get two different prizes ?

- 1. $1/36$
- 2. $1/6$
- 3. $2/6$
- 4. $3/6$
- 5. $5/6$

What is the probability of rolling a **3 or a 4** on a single roll of a die ?

- 1. $1/36$
- 2. $1/6$
- 3. $2/6$
- 4. $3/6$
- 5. $5/6$

What is the probability of rolling snake eyes (two ones) on a single roll of a pair of dice ?

- 1. $1/36$
- 2. $1/6$
- 3. $2/6$
- 4. $3/6$
- 5. $5/6$

Basic Probability

- Additivity Principle
 - If two events are mutually exclusive, the probability of obtaining **one or the other** is the **sum** of their separate probabilities
- Independence Principle
 - The probability of the **joint occurrence** of two or more **independent** events is the product of their separate probabilities

Conditional probability

- The probability of the **joint occurrence** of two **non-independent** events is the **product** of the probability of one event times the probability of the second event **given** that the first event has occurred.
- $P(A \text{ and } B) = P(A) \times P(B|A)$

Bayes' theorem as applied to genetics

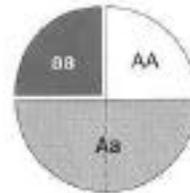
- $P(C|E) = P(C) \times P(E|C) / P(E)$
- Where $P(E) = P(C) \times P(E|C)$

C = genotype E = phenotype, test result, etc.

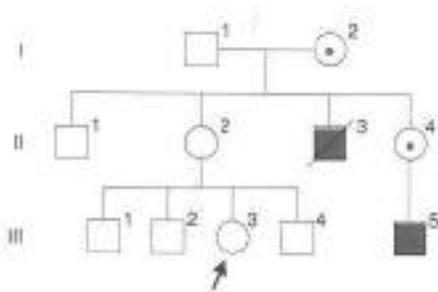
What is the probability that a clinically unaffected sibling of a child with an autosomal recessive disease is a carrier for that disorder ?

Table 12.4. Bayesian Calculation of Carrier Status for an Autosomal Recessive Trait

| | Unaffected Sibling is a Heterozygous Carrier | Unaffected Sibling is Homozygous Normal |
|-------------------------|--|---|
| Prior probability | 1/2 | 1/4 |
| Conditional probability | 1 | 1 |
| Joint probability | $1/2 \times 1 = 1/2$ | $1/4 \times 1 = 1/4$ |
| Posterior probability | $\frac{1/2}{1/2 + 1/4} = 2/3$ | $\frac{1/4}{1/4 + 1/2} = 1/3$ |



What is the probability that the consultand III-3 is a carrier of Duchenne muscular dystrophy ?

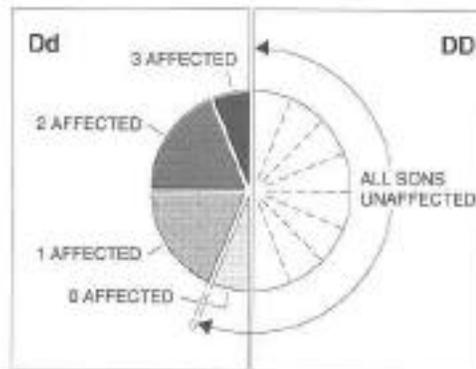
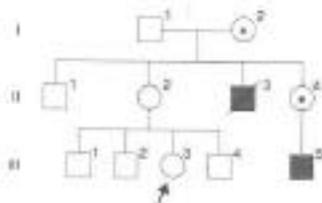


- 1 1/2
- 2 1/4
- 3 1/8
- 4 1/9
- 5 1/18

Table 12.5. Bayesian Calculation of Carrier Status for an X-linked Recessive Trait*

| | <i>II-2 is a Heterozygous Carrier</i> | <i>II-2 is Homozygous Normal</i> |
|-------------------------|---------------------------------------|----------------------------------|
| Prior probability | 1/2 | 1/2 |
| Conditional probability | $(1/2)^3 = 1/8$ | $(1)^3 = 1$ |
| Joint probability | $1/2 \times 1/8 = 1/16$ | $1/2 \times 1 = 1/2$ |
| Posterior probability | $\frac{1/16}{1/16 + 1/2} = 1/9$ | $\frac{1/2}{1/2 + 1/16} = 8/9$ |

*See pedigree in Figure 12.13.



Jane is a 20 year old woman whose 10-year old brother died of GPG disease, a fatal autosomal recessive disease of childhood that has a frequency of 1/40,000 in all populations. Her husband, Dick, is unrelated. What is the probability that their first child will be affected with GPG disease ?

- 1. 1/150
- 2. 1/300
- 3. 1/600
- 4. 1/800
- 5. 1/1200

Jane attends a family reunion at which she is beguiled, bewitched (and becomes pregnant by) Ed, who turns out to be her maternal first cousin! What is the risk that the fetus is affected with GPG disease ?

- 1. 1/150
- 2. 1/48
- 3. 1/32
- 4. 1/24
- 5. 1/12

George, a 20 year-old man, seeks counseling because his paternal grandfather and grandfather's brother died in their 70s from a rare form of cancer that is inherited in an autosomal dominant pattern. George's father died at age 34 in a motor vehicle accident; no medical information or DNA is available. A DNA diagnostic test is developed for this disease; but it detects only 50% of causative mutations. There are no false positive tests. George has a negative test. What is his risk of having this disease ?

- 1. 6%
- 2. 14%
- 3. 25%
- 4. 33%
- 5. 50%