Ah, to be in Ann Arbor, now that dreary November is here….

Bayes' Theorem

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 and B) = P(A) x P(B|A)

Bayes' theorem as applied to genetics

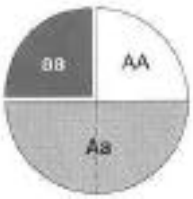
- P(C|E) = P(C) x P(E|C) / P(E)
- Where P(E) = Σ P(C) x P(E|C)

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

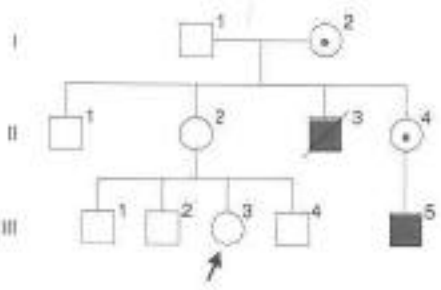
What is the probability that a clinically unaffected sibling of a child with an autosomal recessive disease is a carrier for that disorder ?

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 ?

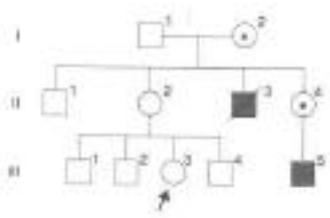


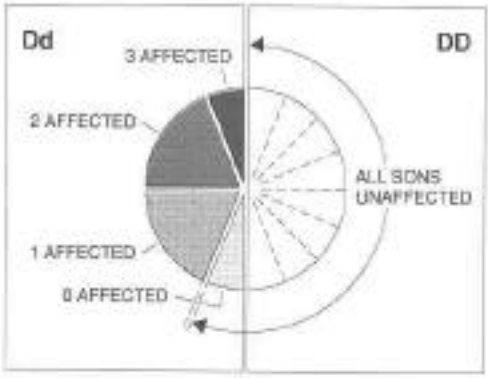
- 1 1/2
- 2 1/4
- 3 1/8
- 4 1/9
- 5 1/18

Table 12.5. Bayesian Calculation of Carrier Status for an X-linked Recessive Trait[a]

	II-2 Is a Heterozygous Carrier	*II-2 Is Homozygous Normal*
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	$\frac{1/16}{1/16 + 1/2} = 1/9$	$\frac{1/2}{1/2 + 1/16} = 8/9$

[a]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%

CLINICAL GENETICS: GENETIC SCREENING

Objectives (Lectures 24-25)

- Understand: **Sensitivity Specificity**
  - **False positive False negative**
- Understand, and be able to calculate, **Positive Predictive Value**
- Understand the types of genetic screening programs and their intent
- Be able to interpret negative test results
- Know the criteria for a successful genetic screening program

Screening Tests in medical practice

- Early diagnosis of treatable/ preventable disease
- Identification of a subset of the population for whom more definitive diagnostic testing should be performed
  - Papanicolaou (Pap) smears
  - mammography
  - hemoccult
  - PPD
  - Blood pressure

Genetic Screening Tests I

- Early recognition of **affected** individuals where early **intervention** is of benefit to affected individual and/or family
  - Common serious diseases of adult life
    - Hypertension, CAD, cancer, hemochromatosis
  - Newborn screening
    - PKU
  - Fetal screening
    - Prenatal diagnosis
    - Multiple marker screening for NTDs, Down syndrome

Genetic Screening Tests II

- Identification of **individuals at risk of transmitting a genetic disease** (i.e. carrier detection)
  - Tay-Sachs disease
  - Hemoglobinopathies
  - Cystic fibrosis

Genetic screening tests Resources

- American College of Medical Genetics
  - http://www.acmg/net
- Pagon RA et al. Online medical genetics resources: a US perspective. British Medical Journal 322: 1035-37, 28 April 2001
- Evans JP et al. The complexities of predictive genetic testing. BMJ 322:1052-56, 28 April 2001
- University of Michigan Medical Genetics Residency Program, Director: Jeffrey Innis MD.PhD <innis@umich.edu>

Problem

- A test to detect a disease has a false positive rate of 5%
- The prevalence of the disease is 1/1000
- What is the chance that person found to have a positive test result actually has the disease ?

- 1. 95%
- 2. 50%
- 3. 20%
- 4. 5%
- 5. 2%

Table 12.6. Outcomes of Screening Tests[a]

	Affected	*Not Affected*
Positive tests	A	B
Negative tests	C	D

[a]False-positive tests are shown in the red-shaded box, false-negatives in the gray-shaded box.

Sensitivity: frequency of positive result when disease is present
A/(A+C)

Specificity: frequency of negative result when disease is absent
D/(B+D)

False positive rate: B/(B+D) = (1- specificity) *NOTE: Book is Wrong !*

False negative rate : C/(A+C)

POSITIVE PREDICTIVE VALUE A/(A + B)

A test to detect heterozygous carriers of a rare AR disease has a **sensitivity of 95%** and **specificity of 95%**. What is the **PPV** in **unaffected siblings** of affected patients, and in the **general population** in which the prevalence of the disease is 1/40,000 ?

Table 12.7. Screening for Heterozygous Carriers among Unaffected Siblings[a]

	Carrier (Dd)	*Normal (DD)*
Positive	64	2
Negative	3	31
Total	67	33

[a]False-positive tests are shown in the red-shaded box, false-negatives in the gray-shaded box. See text for discussion.

Table 12.8. Screening for Heterozygous Carriers in the General Population[a]

	Carrier (Dd)	*Normal (DD)*
Positive	950	4,950
Negative	50	94,050
Total	1,000	99,000

[a]False-positives are shown in the red-shaded box, false-negatives in the gray-shaded box. See text for discussion.

Despite low PPV(16%), screening test identifies a subset of population with 16x increase risk.

Communicating statistical information—natural frequencies

1. Select a population and determine the number of affecteds (prevalence).
2. Use the test's sensitivity to determine how many people have the disease and have a positive test (**true positives**).
3. Use the false positive rate (1 – specificity) to determine how many people do not have the disease but still test positive (**false positives**).
4. Compare the number in step 2 with the sum of those obtained in steps 2 and 3 to determine how many people with a positive test actually have the disease (**Positive Predictive Value**).

Science 290:2261-62 22 Dec 2000)

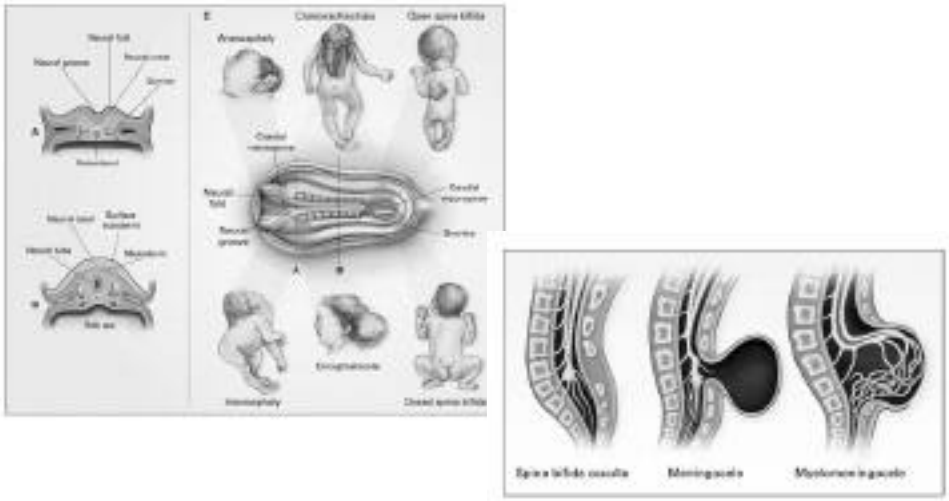
Medical decision making: the problem revisited

- A test to detect a disease has a false positive rate of 5%
- The prevalence of the disease is 1/1000
- **What is the chance that person found to have a positive test result actually has the disease** ?
- The HMS answer (60 students and faculty queried):
  - 27/60 answered 95%
  - 11/60 answered 2%
- The UM answer:
  - 5% of 1000 people have a (false) positive test (~50)
  - 100% of 1 person (with disease) has a (true) positive test
  - **Positive predictive value** = 1/50 = 2%

Cheesehead disease is an autosomal recesssive disease characterized by a bright yellow three-cornered head. It has a **frequency** of 1/1600 in Madison WI, but only 1/1,000,000 in Ann Arbor. A test for heterozygous carriers has a **sensitivity of 90%** and a **specificity of 90%.** 100,000 citizens of each city are screened. What is the **positive predictive value** of a positive test in each city ?

- Madison
  - *2pq = 1/20
  - *5,000 carriers,
    4,500 with +ive result
  - *95,000 non-carriers,
    9,500 with +ive result
  - *PPV Madison is
    4500/14,000 = 32%
- Ann Arbor
  - *2pq = 2/1000
  - *200 carriers,
    180 with +ive result
  - *99,800 non-carriers,
    9,980 with +ive result
  - *PPV Ann Arbor is
    180/10,160 = <2%

Neural Tube Defects

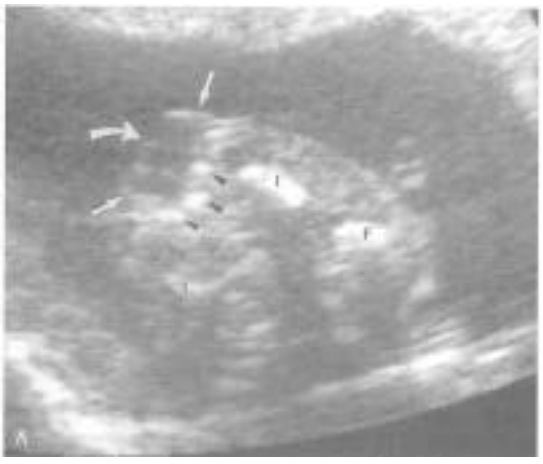


Closure by 28 days

Maternal Serum Alpha-Fetoprotein (MSAFP)

- NTDs: ~1/1000 liveborns
  - Recurrence risk ~1/100
  - 95% of LBs with NTDs born to moms without prior hx
- Amniotic fluid AFP elevated in open NTDs (1972)
- Maternal serum AFP also increased
  - 2 consecutive ↑ MSAFP @ 16-18 weeks =1/20 risk
  - Can detect 80-85% open NTDs by ↑ MSAFP
  - F/U with amniocentesis or high resolution ultrasound

NTD--ultrasound



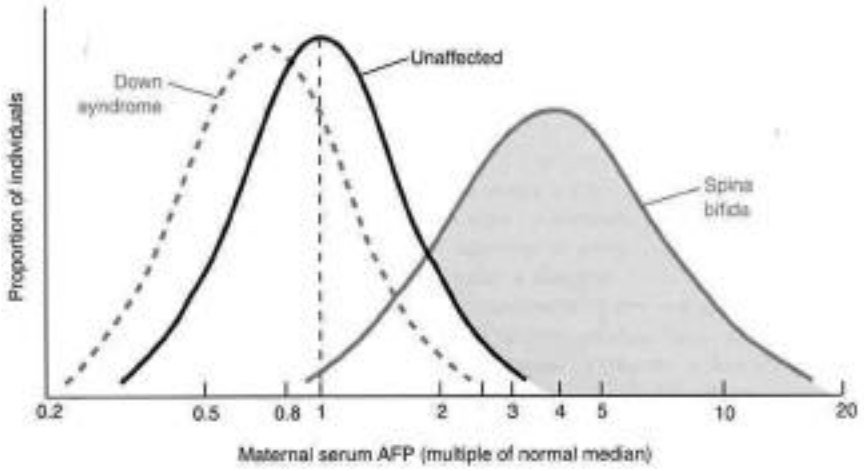
NTDs—results of MSAFP

Fig. 27-1. Prevalence of neural tube defects at birth in England and Wales 1964–1993.

Maternal Serum Alpha-Fetoprotein (MSAFP)

- NTDs: ~1/1000 liveborns
  - Recurrence risk ~1/20
- Amniotic fluid AFP elevated in open NTDs
- Maternal serum AFP also increased
  - 2 consecutive ↑ MSAFP @ 16-18 weeks =1/20 risk
  - Can detect 80-85% open NTDs by ↑ MSAFP (1.5% FPR)
  - F/U with amniocentesis or high resolution ultrasound
- PREVENTION WITH FOLIC ACID
  - –400 mcg/d decreases incidence by >70%

MSAFP in Down syndrome



Multiple marker screening for chromosomal aneuploidy

- ↓MSAFP in women carrying fetus with Down syndrome
- ↓MSAFP plus ↑hCG and ↓unconjugated E3 (Multiple Marker Screening) allows diagnosis of ~50% of DS in mothers <35 (75% of babies with DS born to women <35)
- MM screening can detect ~85-90% of DS fetuses in women >35
- MM screening @ 16 weeks detects ~75% of Down syndrome fetuses with 5% FPR

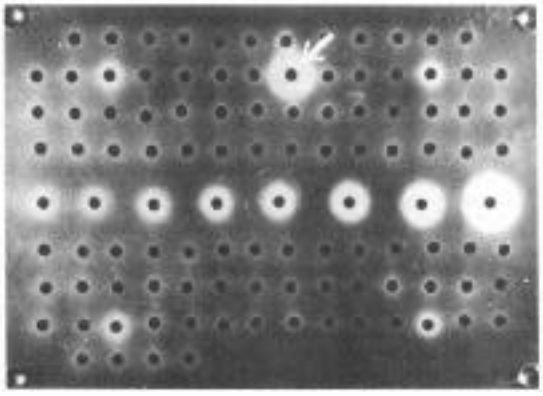
First trimester screening for DS

- Nuchal translucency by ultrasound +
- Pregnancy-associate plasma protein A +
- Free B-hCG -
  - Detection of ~85-90% of DS with false positive rate of 5% in one study

Newborn Screening

- Population based
- Mandated by law
- Phenylketonuria (PKU)
  - Guthrie Test (1962):

Guthrie Test



Newborn Screening

- Phenylketonuria (PKU)
  - Guthrie Test (1962): high sensitivity, low specificity.
    - PPV ~ 5%.
    - Need for specific Dx tests
  - "Eliminated" MR caused by PKU
  - "Maternal PKU"

Michigan screening program

Table 12.9. Michigan Newborn Screening Program

Disease	Inheritance	Incidence	Screening Test	Treatment
Phenylketonuria (PKU)	AR	1/18,000	Rapid flow fluorometric assay (RFA)	Dietary restriction of phenylalanine
Congenital hypothyroidism	Usually sporadic	1/4,000	Radioimmunoassay of T4	Thyroid hormone replacement
Sickle cell anemia	AR	1/2,800 (1/400 blacks)	High performance liquid chromatography	Close medical care, penicillin prophylaxis
Congenital adrenal hyperplasia (CAH)	AR	1/14,000	Immunofluorometric assay of 17-OH progesterone	Cortisol
Galactosemia	AR	1/60,000 to 1/100,000	RFA for galactose and galactose-1-phosphate	Soy formula, galactose restriction
Biotinidase deficiency	AR	1/60,000 to 1 /100,000	Enzymatic assay (colorimetric)	Pharmacologic doses of biotin
Maple syrup urine disease (MSUD)	AR	1/200,000 to 1/250,000	Bacterial inhibition assay (detects leucine)	Dietary restriction of branched-chain amino acids

AR, autosomal recessive

Tandem mass spectrometry

Predictive genetic testing

- Conventional medical diagnostic test
  - Individual patient
  - Current status
- Predictive genetic test
  - Direct implications for family members
  - Future condition (that may or may not develop)
  - ??whether ??when ??how severe ?? Benefits of intervention
- Usually not determinative

The last well person

CK Meador, NEJM 330:440-42, 1994

- "The demands of the public for definitive wellness are colliding with the public's belief in a diagnostic system that can find only disease. A public in dogged pursuit of the unobtainable, combined with clinicians whose tools are powerful enough to find very small lesions, is a setup for diagnostic excess. And false positives are the arithmetically certain result of applying a disease-defining system to a population that is mostly well."

Predictive genetic testing for presymptomatic /predisposed individuals

- MEN2
  - Full penetrance, thyroid Ca
- Colorectal cancer
  - Colonoscopy surveillance
- Breast cancer
  - ?? Penetrance
  - ?? Treatment options
- Hemochromatosis
  - Low penetrance
  - Modifiers: sex, diet, alcohol
  - Phenotypic screening

Hereditary Hemochromatosis

- **Common** 2-5/1000
- AR, iron overload
- **Clinically serious**
  - liver cirrhosis and 1^{o} hepatic carcinoma
  - diabetes mellitus
  - cardiomyopathy
  - endocrinopathy
  - arthropathy
- **Treatable**: phlebotomy

Hereditary Hemochromatosis-2

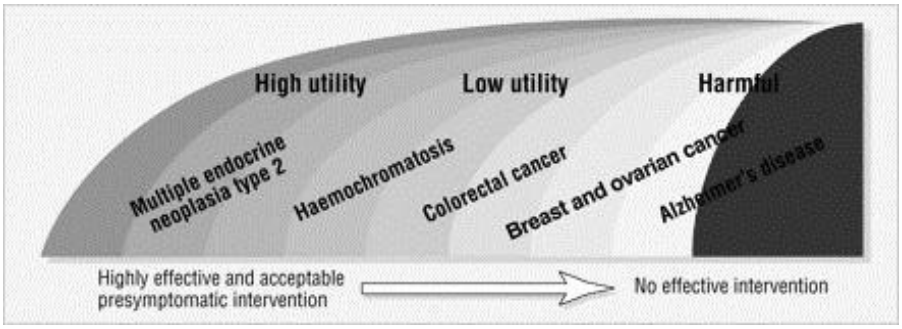
- Modifiers of Phenotype
  - Sex (protective effect of menses, pregnancy)
  - Dietary iron vs blood loss
  - Alcohol intake

  - Mendelian disease that behaves like a common complex disease

Hereditary Hemochromatosis-3

- Why not screen everyone ?
- Gene test available: *HFE* on chromosome 6
  - C282Y high penetrance
  - H63D low penetrance, common
- Phenotypic screening available
  - Iron, TIBC, ferritin
- What does a positive test mean ?
- Family screening vs Population screening

Utility of testing



–Evans et al. BMJ 322:1052-56 (2001)

Screening for carriers of recessive genetic diseases: Criteria for a cost –effective program

- Clinically significant disease that warrants screening
- High-risk population that is receptive
- Inexpensive test with adequate sensitivity and specificity
- Definitive test for specific diagnosis
- Reproductive options available
- Counseling and education

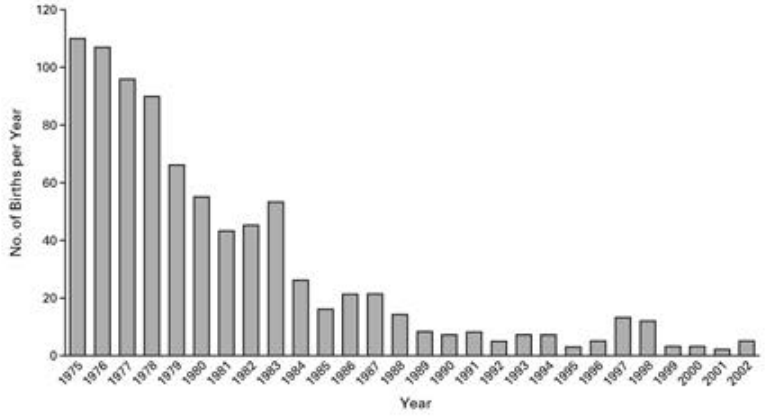
Carrier Screening in selected populations

Population	Disorder	Test	Carrier Frequency
Ashkenazi Jewish	Tay-Sachs disease	Enzyme/DNA	1/30
	Cystic fibrosis	DNA	1/29
	Gaucher disease	DNA	1/15
	Canavan disease	DNA	1/40
French Canadian	Tay-Sachs disease	DNA	1/70
Asian	Thalassemia	Hematologic	Population-specific
Mediterranean	Thalassemia	Hematologic	Population-specific
African	Sickle cell anemia	Hematologic	1/10
White	Cystic fibrosis	DNA	1/25

Carrier screening programs

- Tay-Sachs Disease
  - Community based
  - 3 mutations account for 98% of Ashkenazi cases
  - Frequency in this population decreased by 90%
- Beta-thalassemia in Sardinia,Italy,Cyprus,Greece
  - Voluntary, frequency decreased by 95%
- Cystic Fibrosis
  - A much more complex issue
  - *American College of Obstetricians and Gynecologists & American College of Medical Genetics (2001). Preconception and Prenatal Carrier Screening for Cystic Fibrosis: Clinical and Laboratory Guidelines. Washington, DC: American College of Obstetricians and Gynecologists. http://www.acog.org/from_home/wellness/cf001.htm*

_-thalassemia screening in Sardinia



Implications of genetic screening tests for health and social policy

- Role of the primary care physician
- Role of commercial laboratories
- What diseases ?
- Insurance
- Employment discrimination
- Self-image
- Public health policy (reduction in the frequency and burden of genetic diseases)
  - Versus **Individual autonomy**

HJ, an 8 year-old boy , is brought by his mother for *APC* testing. His paternal grandfather died at 53 of colorectal carcinoma and had familial adenomatous polyposis (FAP). HJ's paternal uncle also died from this disease. HJ's father was killed in a motor vehicle accident at age 22. No blood or tissue is available from any of these deceased relatives. *APC* gene testing, by protein truncation test (PTT) can detect 80% of affected families. PTT testing for *APC* mutations in HJ reveals no mutation causing protein truncation. What is the risk that **HJ is affected with FAP** ?

A. 0%
B. 6%
C. 20%
D. 25%
E. E. 40%

Tissue is found from HJ's father and paternal grandfather. Protein truncation testing reveals a mutation causing truncation in each. Now what is the risk that HJ (who had a negative test) is affected with FAP ?

- A. 0%
- B. 6%
- C. 20%
- D. 40%
- E. 50%