Population genetic screening

Principles and applications

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Definition: Population Screening

Presumptive identification of unrecognized disease by application of tests, examination, and other procedures.

The procedures can be applied to rapidly sort out "apparently"well individuals who probably have a disease from those who probably do not.

The procedures are not intended to provide a definitive diagnosis.

Definition: Genetic screening

Identification of individuals possessing certain *genotypes* that either are (A) associated with disease or predisposition, or (B) which lead to disease in their descendants.

Examples:
(A) Newborn screening for metabolic disease

(B) Heterozygote detection of Tay-Sachs or Gaucher disease

Objectives of genetic screening

- Early recognition of disorder:
  for intervention that prevents or reverses the disease process,

  or to ensure optimal management of the patient, eg. appropriate referrals to specialists when symptoms are anticipated
- Informed reproductive decisions/ disease management, eg. trisomies 13 and 18, which are generally lethal in the newborn period.

Principles of screening

Disease

1. Disease is serious and relatively common - cost/benefit
2. Natural history well defined
3. Acceptable and effective treatment
4. Prenatal diagnosis available for some conditions

Test

1. Inexpensive
2. Valid and reliable
3. Easy to perform
4. “Socially acceptable”

Principles of screening (continued)

System

1. Resources for diagnosis/treatment accessible.
2. Results communicated efficiently and effectively.
3. At-risk population can then be targeted with more accurate, often more expensive subsequent tests.

Box 13-1
Genetic Screening and Prenatal Diagnosis

I. Population screening of genetic disorders
- A. Newborn Screening
  1. Blood
     - a. PKU, all 50 states in the United States
     - b. Galactosemia, all 50 states in the United States
     - c. Hypothyroidism, all 50 states in the United States
     - d. Other: hemoglobinopathies, cystic fibrosis
  2. Urine: aminoacidopathies
- B. Heterozygote Screening
  1. Tay Sachs disease, Ashkenazi Jewish population
  2. Sickle cell disease, African American population
  3. Thalassemias, at risk ethnic groups
  4. Cystic fibrosis, pilot programs only

II. Prenatal diagnosis of genetic disorders
- A. Diagnostic testing (invasive prenatal diagnosis)
  1. Amniocentesis
  2. Chorionic villus sampling
  3. Percutaneous umbilical cord sampling (PUBS)
- B. Fetal visualization techniques
  1. Ultrasonography
  2. Radiography
  3. MRI
- C. Population screening
  1. Maternal age > 35 years
  2. Family history of condition diagnosed by prenatal techniques
  3. Abnormal maternal serum α fetoprotein estriol, human chorionic gonadotropin

III. Family screening of genetic disorders
- A. Family history of chromosomal rearrangement (e.g. translocation)
- B. Screening female relatives in an X-linked pedigree (e.g. Duchenne muscular dystrophy, Fragile X syndrome
- C. Heterozygote screening within at-risk families (e.g. cystic fibrosis)
- D. Presymptomatic screening (e.g. Huntington disease, breast cancer, colon cancer)

How useful is a screening test?

Table 13-1 Definitions of Sensitivity and Specificity*

	Disease State	
Screening test	Affected	Unaffected
Results positive (+)	a (true positive)	b (false negative)
Results negative (-)	c (false negative)	d (true negative)

*Sensitivity = a/ (a + c); specificity = d/ (b + d)

Propotion of true positives Proportion of true negatives

Accuracy: what is the proportion of persons with a positive test who truly have the disease in question? Termed the positive predictive value.

Benefit of a screening test is also related to it's positive predictive value.

TABLE 13-2 Hypothetical Results of Screening for Congenital Adrenal Hyperplasia in a Low-Prevalence Caucasian Population and a High Prevalence Yupik Population*

	CAH PRESENT		CAH ABSENT	
Screening Test	Positive	Negative	Positive	Negative
Caucasian	47	3	5,000	494,950
Yupik	24	1	100	9,875

*Caucasian positive predictive value = 47/ (47 + 5,000) = 1%
Yupik positive predictive value = 24/ (24 + 100) = 19%

The *positive predictive value* is different from *sensitivity*.

Prenatal testing

Benefits include:

- Reassurance to at-risk families when results are normal
- Providing risk information to couples who without the info might not choose to begin a pregnancy
- Allowing couple to prepare for birth of an affected baby
- Help health care professional plan delivery, management of an affected infant prior to birth.
- Providing risk information to couples for whom pregancy termination is an option.

98% of prenatal diagnoses yield a normal test result.

The majority of families receive reassurance; only a small minority face the issues of delivery of an affected child or termination.

Ultrasound: noninvasive screening procedure to visualize the fetus

Selected Disorders Diagnosed By Ultrasound in the Second Trimester*

System Complex

Hydrops
Oligohydramnios
Polydramnios
Intrauterine growth retardation

Central Nervous System

Anencephaly (85-90%)
Encephalocele
Holoprosencephaly
Hydrocephalus

Craniofacial

Cleft lip

Chest

Congenital heart disease
Diaphragmatic hernia

Abdomen/ Pelvis

Gastrointestinal atresias
Gastroschisis
Omphalocele
Renal agenesis
Cystic Kidneys
Hydronephrosis

Skeletal System

Limb reduction defects
Many chondrodystrophies, including thanatophoric dysplasia and osteo-genesis imperfecta

Overall: 30-50% sensitivity
99% specificity

*Detection rate varies by condition

Chorionic villus sampling (CVS)-

aspirating fetal trophoblasts either trans-cervically or -abdominally

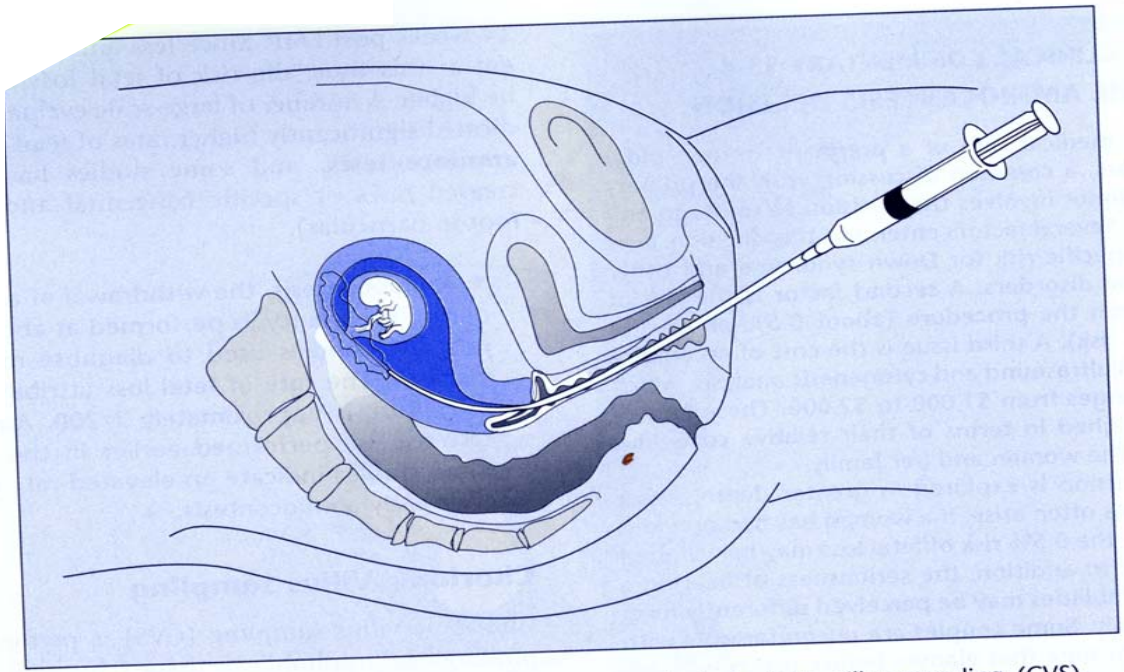


FIG. 13-5 A schematic illustration of a transcervical chorionic villus sampling (CVS) procedure. With ultrasound guidance, a catheter is inserted, and several milligrams of villus tissue are aspirated.

- CVS performed at 10-11 weeks vs 15-17 weeks for amniocentesis after last menstrual period. More rapid results generally.
- Risk of fetal loss is higher than amnio procedure: 1-1.5%
- Confined placental mosaicism (in extraembryonic tissue only): 1-2%
- Possible limb shortening when CVS performed early (<10 weeks).

Amniocentesis - a diagnostic test:

At 15-17 weeks after last menstrual period,
a needle in abdominal wall into amniotic sac guided by real-time ultrasound.
Amniocytes are cultured and cytogenetic (chromosomal studies) are performed.
Results usually available in 10-12 days.

Risk of fetal loss due to procedure 0.5%. Women <35 yrs of age: probability of loss due to amnio > probability of detecting a diagnosable condition.

Box 13-3	**Indications for Prenatal Diagnosis by Amniocentesis**

Maternal age> 35 years

Previous child with chromosome abnormality

History of structural chromosome abnormality in one of the parents

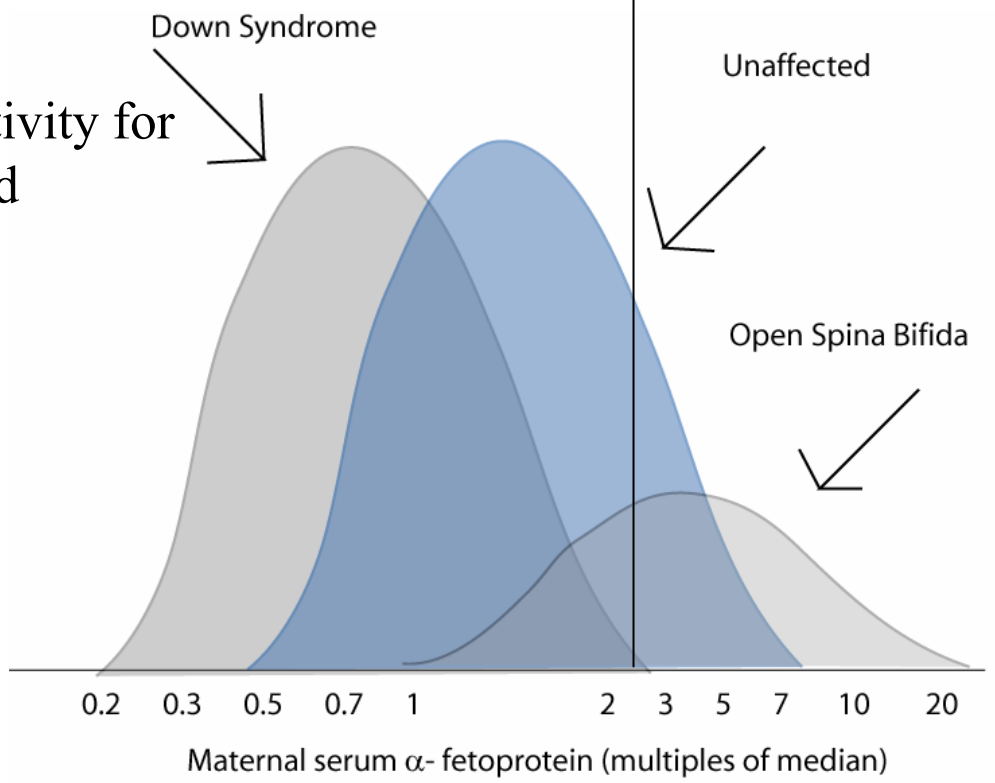
Family history of genetic defect that is diagnosable by biochemical or DNA analysis

Risk of neural tube defect (NTD)

Alpha fetoprotein screening

>2 MOM is “increased”

40% sensitivity for those tested



80% sensitivity

MSAFP levels in mothers carrying normal fetuses vs. fetuses with Down syndrome or open spina bifida. It is lowered in Down syndrome somewhat, and substantially increased in spina bifida.

Low pos.predictive value (6%), but justified because 90-95% NTD have no family history.

Better sensitivity for Down syndrome screening is achieved with triple test of:

MSAFP,
serum unconjugated estriol,
and
chorionic gonadotropin.

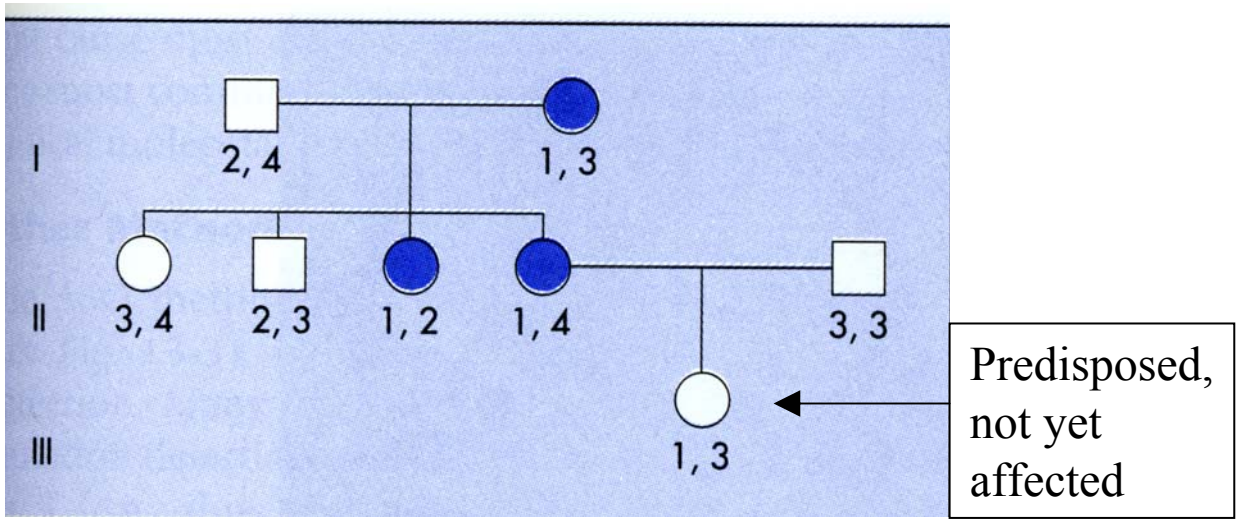
MSAFP alone = 40% of Down syndrome pregnancies.
All three = 70% (false positive rate of 5%).

Table 13-5 Selected Single-Gene Disorders for Which Family Screening and Prenatal Diagnosis by DNA are Available

Disease	DNA Analysis
Neurofibromatosis type 1	Linkage analysis/ direct mutation analysis
Myotonic dystrophy	Direct mutation analysis
Cystic fibrosis	Direct mutation analysis
Sickle-cell disease	Direct mutation analysis
Fragile X syndrome	Direct mutation analysis
Hemophilia A	Direct mutation analysis/ linkage analysis
Huntington disease	Direct mutation analysis
Duchenne muscular dystrophy	Direct mutation analysis/ linkage
Familial breast cancer	Direct sequencing/ linkage
Hemochromatosis	Direct mutation analysis

Screening for disease predisposition by genetic linkage analysis

Age-related expression, eg. breast cancer



Test direct descendants and relatives of affected individual using genetic marker closely linked to disease locus. Grandmaternal allele 1 is linked to the disease allele in this family. If III-1 were tested, this would be a *presymptomatic* test.

Table 13-6	Selected Inborn Errors of Metabolism That are Diagnosable Through Amniocentesis and/ or CVS
Disease	Measurable Enzyme
Disorders of Amino Acid/ Organic Acid Metabolism	
Maple syrup urine disease	Branched-chain ketoacid decaboxylase
Methylmalonic academia	Methylmalonic CoA mutase
Multiple caboxylase deficiency	Biotin responsive carboxylase
Disorders of Carbohydrate Metabolism	
Glycogen storage disease, type 2	α-Glucosidase
Galactosemia	Galactose-1-uridyl transferase
Disorders of Lysosomal Enzymes	
Gangliosidosis (all types)	β-Galactosidase
Mucopolysaccharidosis (all types)	Disease-specific enzyme
Tay-Sachs disease	Hexosaminidase
Disorders of Purine and Pyrimidine Metabolism	
Lesch-Nyhan syndrome	Hypoxanthine-guanine phosphoribosyl transferase
Disorders of Peroxisomal Metabolism	
Zellweger syndrome	Long-chain fatty acids

Newborn genetic screening

- Opportunity for presymptomatic detection and intervention

- All states screen newborns for
  PKU,
  galactosemia and
  hypothyroidism
  Mental retardation in these conditions
  can be prevented by early detection and effective intervention.

- Other screening programs include hemoglobinapathies (up to 15% with HbS die of infections before age 5), muscular dystrophy, and other rare biochemical disorders that are prevalent in local groups (Glycogen storage disease type II, MSUD, methylmalonic acidemia in Amish).

Table 13-3 Characteristics of Selected Newborn Screening Programs

Disease	Inheritance	Prevalence	Screening Test	Cost	Treatment
Phenylketonuria	Autosomal recessive	1/10,000-1/15,000	Guthrie test	$1.25	Dietary restriction of phenylalanine
Galactosemia	Autosomal recessive	1/50,000-1/100,000	Transferase assay	$1.00	Dietary restiction of galactose
Congenital Hypothyroid	Usually sporatic	1/5,000	Measurement of T4 or TSH	$1.50	Hormone replacement
Sickle cell disease	Autosomal recessive	1/400-1/600 African Americans	Isoelectric focusing or DNA diagnosis	$1.50	Prophylactic penicillin

Heterozyogote screening

- Target population: group known to be at risk - often an ethnic background
- Intervention: presentation of risk figures, option of prenatal diagnosis
- Candidate disorders are generally:
  - autosomal recessive,
  - prenatal diagnosis and counseling are available, feasible and accurate

Phenylketonuria

1 in 10-15K births
Untreated, 95% become moderately/severely MR.
Not identified clinically in 1st year of life
Dietary treatment usually (except those with biotin synthesis defect) results in normal intelligence.

Guthrie test: blood incubated with Phe-deficient B. subtilis strain. Growth is related to PHE levels.
Test must be confirmed by repetition, since sensitivity depends on diet.

Box 13-2 **Public Policy Guidelines for Heterozygote Screening**

Recommended Guidelines:

1. Screening should be voluntary, and confidentiality must be ensured.

2. Screening requires informed consent.

3. Providers of screening services have an obligation to ensure that adequate education and counseling are included in the program.

4. Quality control of all aspects of the laboratory testing, including systematic proficiency testing, is required and should be implemented as soon as possible.

5. There should be equal access to testing.

From Elias S, Annas G, Simpson JL (1991) Carrier screening for cystic fibrosis: implications for obstetric and gynecologic practice. Am J Obstet. Gynecol. 164: 1077-1083.

Table 13-4 Selected Examples of Heterozygote Screening Programs in Specific Ethnic Groups

Disease	Ethnic Group	Carrier Frequency	At-risk couple frequency	Disease incidence in newborns
Sickle-cell disease	African-Americans	1/12	1/150	1/ 600
Tay-Sachs disease	Ashkenazi Jews	1/30	1/900	1/ 3,600
β- Thalassemia	Greeks, Italians	1/30	1/900	1/ 3,600
α- Thalassemia	Southeast Asians and Chinese	1/25	1/625	1/ 2,500
Cystic Fibrosis	Northern Europeans	1/25	1/625	1/ 2,500

Accurate carrier testing for **Tay-Sachs** (HEXA) has reduced number of newborns 90% since 1970. Tay Sachs resuls in accumulation of GM2 ganglioside which leads to blindness, seizures, hypotonia, and death by age 5.

CF screening is about to be recommended for Caucasians by Am. College of Ob/Gyn, but has not by American College of Med Genetics. Cost/benefit is less clear-cut. (1/600 couples would be heterozygotes, 1/2400 affected). Counseling requirements would be impractical.

Summary

- Genetic screening and testing are well accepted by health care professionals and patients for certain conditions.
- Criteria for screening and/or testing include (a) benefits to the patient, (b) test accuracy, sensitivity and specificity, and (c) availability of resources for diagnosis and treatment and a system for communicating results efficiently and effectively.
- Prenatal, newborn and heterozygote screening and testing are available