Genetic Testing and Prenatal Diagnosis

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Key Points

- Many types of genetic testing exist
- ID genetic disorders in fetuses, newborns, and adults
- Cells are analyzed for heritable disorders
- Adults can be tested for many genetic disorders
- Some genetic conditions can be treated
- Test results often create privacy issues

Indications for genetic counseling:

- Advanced parental age
  - Maternal age > 35 years
  - Paternal age > 50 years
- Child with congenital anomalies or dysmorphology
- Consanguinity or incest

Family history of heritable disorders or diseases , including:

- Adult onset
- Complex/multi factorial inheritance
- Chromosomal abnormality
- Single gene disorders
- Heterozygote screening based on ethinicity, including:
- Sickle cell anemia (W.African, Mediterranean, Arab,Indo- Pakistani, Turkish , S.E Asian .
- Tay-sachs , canavan (Ashkenazi - Jewish , French - Canadian)
- Thalassemias (Mediterranean, Arab, Indo-Pakistani.)

Abnormalities in pregnancy screening :

- Maternal serum screens
  - Maternal serum dual screen carried out between 10-14 weeks; free beta human chorionic gonadotropin (free beta hCG) and pregnancy associated plasma protein-A (PAPP-A) and nuchal translucency (NT).
  - Maternal serum triple screen carried out between 16-18 weeks (alpha fetoprotein, β-hCG,, estriol)
  - Quatruble screen (alpha fetoprotein, β-hCG, estriol, h-hCG) and inhibin-A)
- Abnormal Prenatal ultra sound examination
- Still born with congenital anomalies and/orAbnormal fetus pregnancy history
- Teratogen exposure or risk

Steps of the genetic counseling process:

- Information gathering
- Diagnosis- based on accurate family history, medical history,
- Examination and investigations
- Risk assessment
- Information giving
- Psycholocgical assesment ad counseling
- Discussion of options
- Help with desicion making
- On going client support

Diagnosis:

- A full and accurate family history is a corner stone in the genetic assessment and counseling process.

- The 1st and most important step in the diagnosis of genetic disorders is construction of a family tree.

- The pattern of inheritance can be shown from the pedigree
  - for eg: vertical transmission in autosomal dominant disorders, horizontal transmission in autosomal recessive disorders and oblique transmission in X-linked recessive disorders

Who needs Genetic Testing

- ID people who:

  1. May have or may carry a genetic disease

  2. Are at risk of having a child with a genetic disorder

  3. May have a genetic susceptibility to drugs and environmental agents

Genetic Screening

- Large populations vs. individuals

- ID individuals who are in the following groups:

  1. May have or may carry a genetic disease

  2. Are at risk of having a child with a genetic disorder

Impact of Genetic Testing

- Discovery of other affected or at-risk individuals
- ID someone who will develop serious or fatal genetic disorders in later life
  - Often has serious personal, family, and social effects
- Direct impact on the children or grandchildren of the person being tested

Types of Genetic Testing

1. **Prenatal diagnosis:** determine genotype of fetus

2. **Carrier testing:** test family members, determine chances of having an affected child

3. **Presymptomatic testing:** ID individuals who will develop disorders in midlife

Prenatal Genetic Testing

- Detect genetic disorders and birth defects
- > 200 single gene disorders can be diagnosed
- Testing done only when a family history or other risk

Genetic Disorders

Table 7.1 Genetic Disorders

Disorder	Incidence	Inheritance Pattern
Cystic fibrosis	1 in 3300 Caucasians	Autosomal recessive
Congenital adrenal hyperplasia	1 in 10,000	Autosomal recessive
Duchenne muscular dystrophy	1 in 3500 male births	X-linked recessive
Hemophilia A	1 in 8500 male births	X-linked recessive
Alpha and beta thalassemia	Varies	Autosomal recessive
Huntington disease	4–7 in 100,000	Autosomal dominant
Polycystic kidney disease	1 in 3,000	Autosomal dominant
Sickle cell anemia	1 in 400 African Americans	Autosomal recessive
Tay-Sachs disease	1 in 3600 Ashkenazi Jews and French Canadians; 1 in 400,000 in the general population	Autosomal recessive

Ultrasound

- Noninvasive, uses reflected sound waves converted to an image
- **Transducer** placed on abdomen
- See physical features of fetus, not chromosomes
- May ID some chromosomal abnormalities by physical features

Woman Having an Ultrasound

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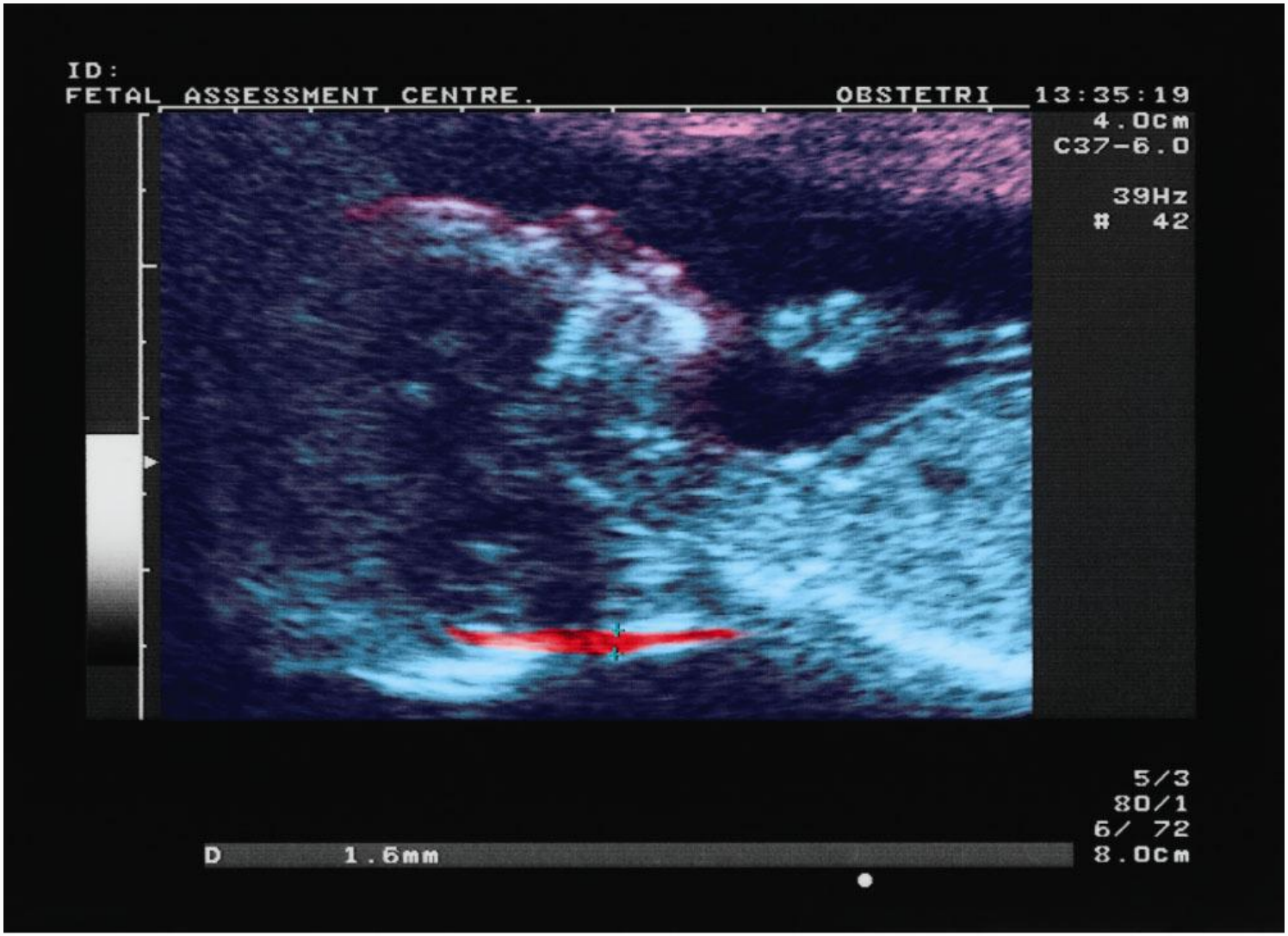
Ultrasound of Fetus with Neck Fold



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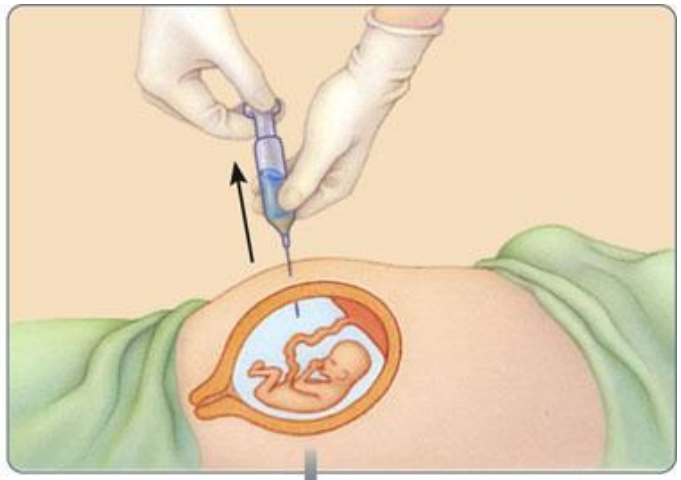
Amniocentesis

- Diagnose > 100 disorders, cells analyzed for chromosomal and biochemical disorders
- Risk of infection and spontaneous abortion
- Normally only used when:
  - Advanced maternal age
  - History of chromosomal disorder
  - Parent with chromosomal abnormality
  - Mother carrier of X-linked disorder

Removal of about 20 ml of amniotic fluid containing suspended cells that were sloughed off from the fetus



Centrifugation

Biochemical analysis of the amniotic fluid after the fetal cells are separated out

Fetal cells are removed from the solution

Analysis of fetal cells to determine sex

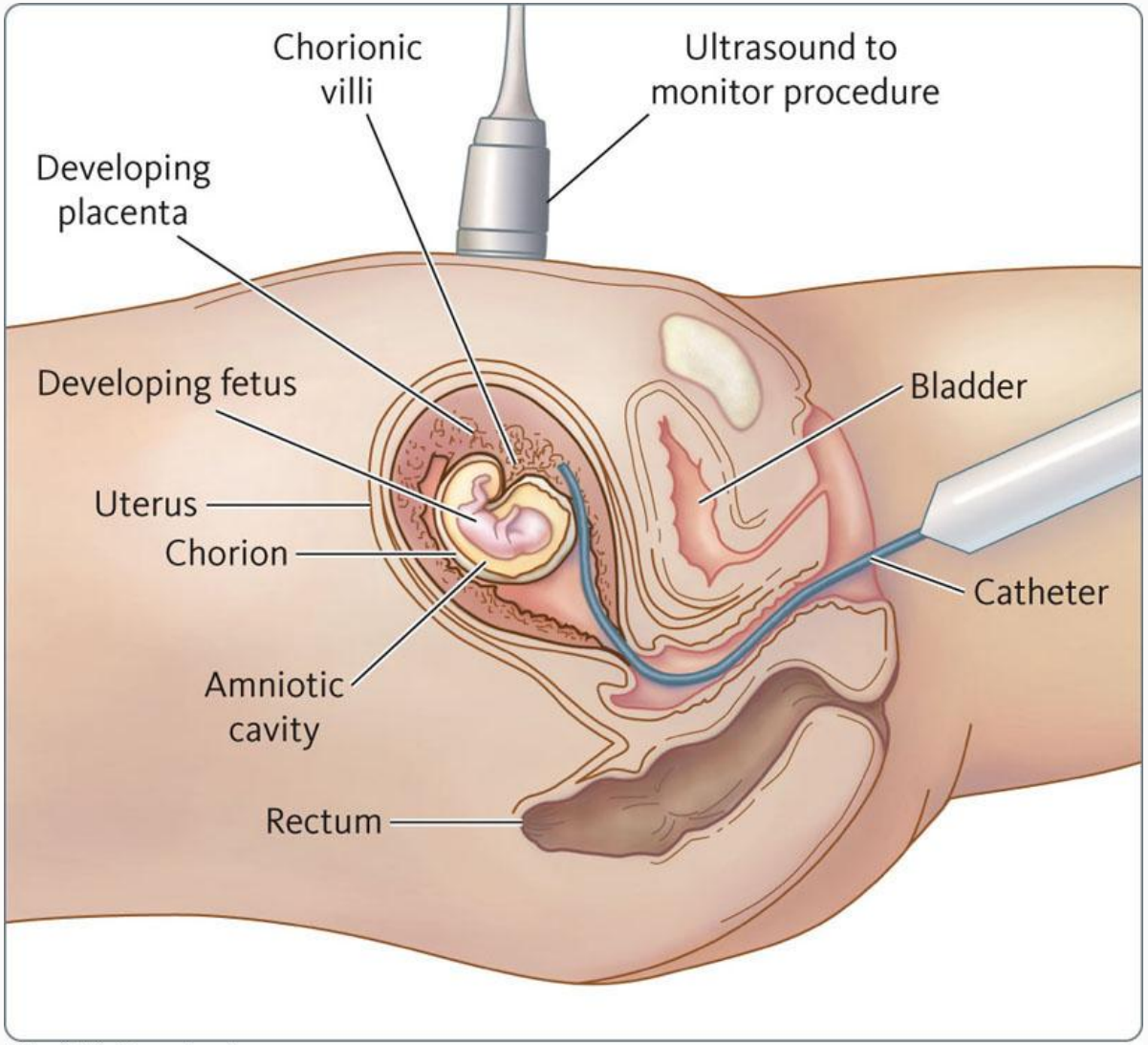
Cells are grown in an incubator

Karyotype analysis

Chorionic Villus Sampling (CVS)

- Done for similar reasons as amniocentesis
- Performed earlier than amniocentesis
  - 6–10 weeks vs. 16 weeks
- Karyotypes available within a few hours or days
- Increased risk of spontaneous abortion (.5–2%)

Review of CVS Procedures



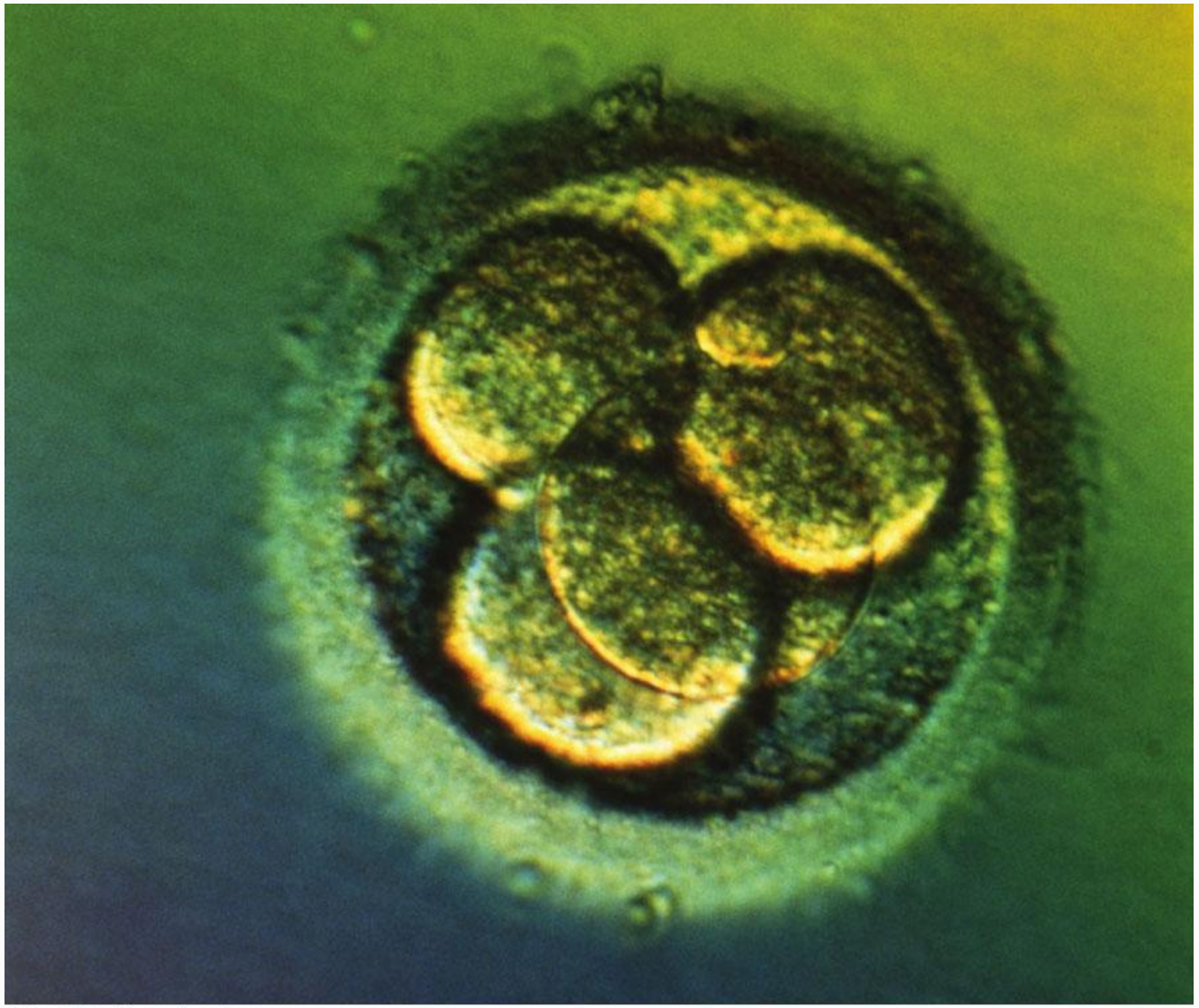
Fetal Cells in Maternal Circulation

- Types
  - Placental cells
  - White blood cells
  - Immature red blood cells with nuclei
- Enter the bloodstream (~6 and 12 weeks)
- Fetal cells, only 1/100,000 in mother's blood
- Techniques need to be developed

Preimplantation Genetic Diagnosis (PGD)

- Eggs collected, fertilized, allowed to develop
- ~Third day of fertilization, embryo has 6–8 cells
- For PGD, one cell, a **blastomere,** is removed
- DNA extracted and tested
- Embryo without genetic disorder are implanted into mother

Embryo - Blastomere



Fetal Cells Analyzed

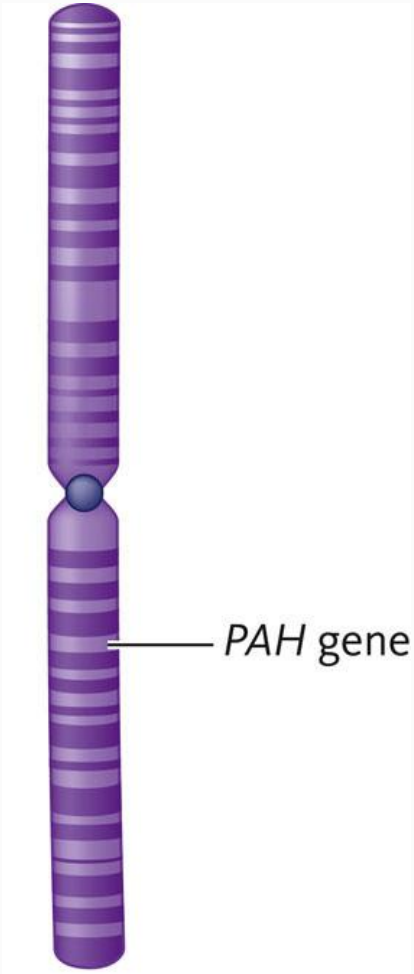
- Several methods including:
  - Karyotyping
  - Biochemical analysis
  - Recombinant DNA techniques

- DNA analysis is most specific and sensitive

Prenatal Diagnosis of PKU

- Gene for PKU, **PAH** on chromosome 12
- Cannot convert **phenylalanine** into **tyrosine**
- Inactivates phenylalanine hydroxylase (PAH)
- Damage from phenylalanine build up
- Genetic and environmental disease

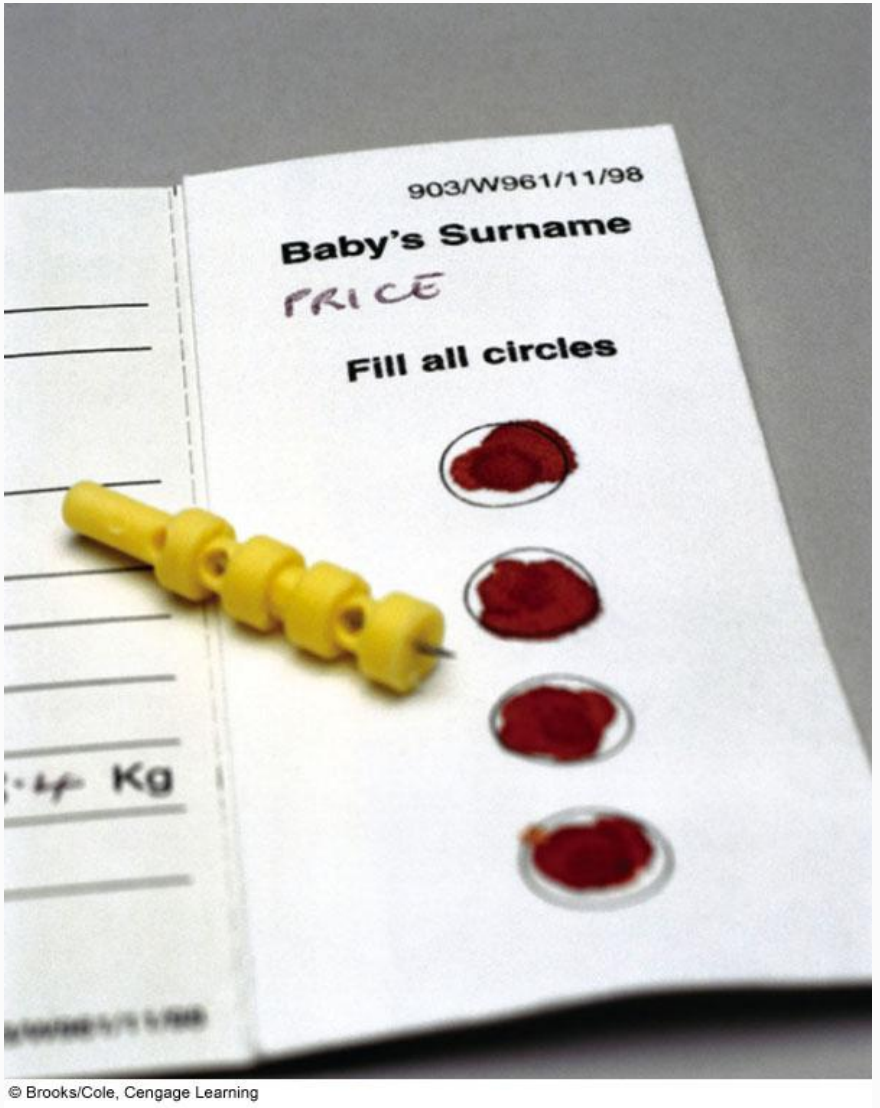
PAH on a Chromosome Map



Chromosome 12

Testing for PKU

- Many different mutations hard to find
- State testing of newborns important



Adults for Genetic Conditions

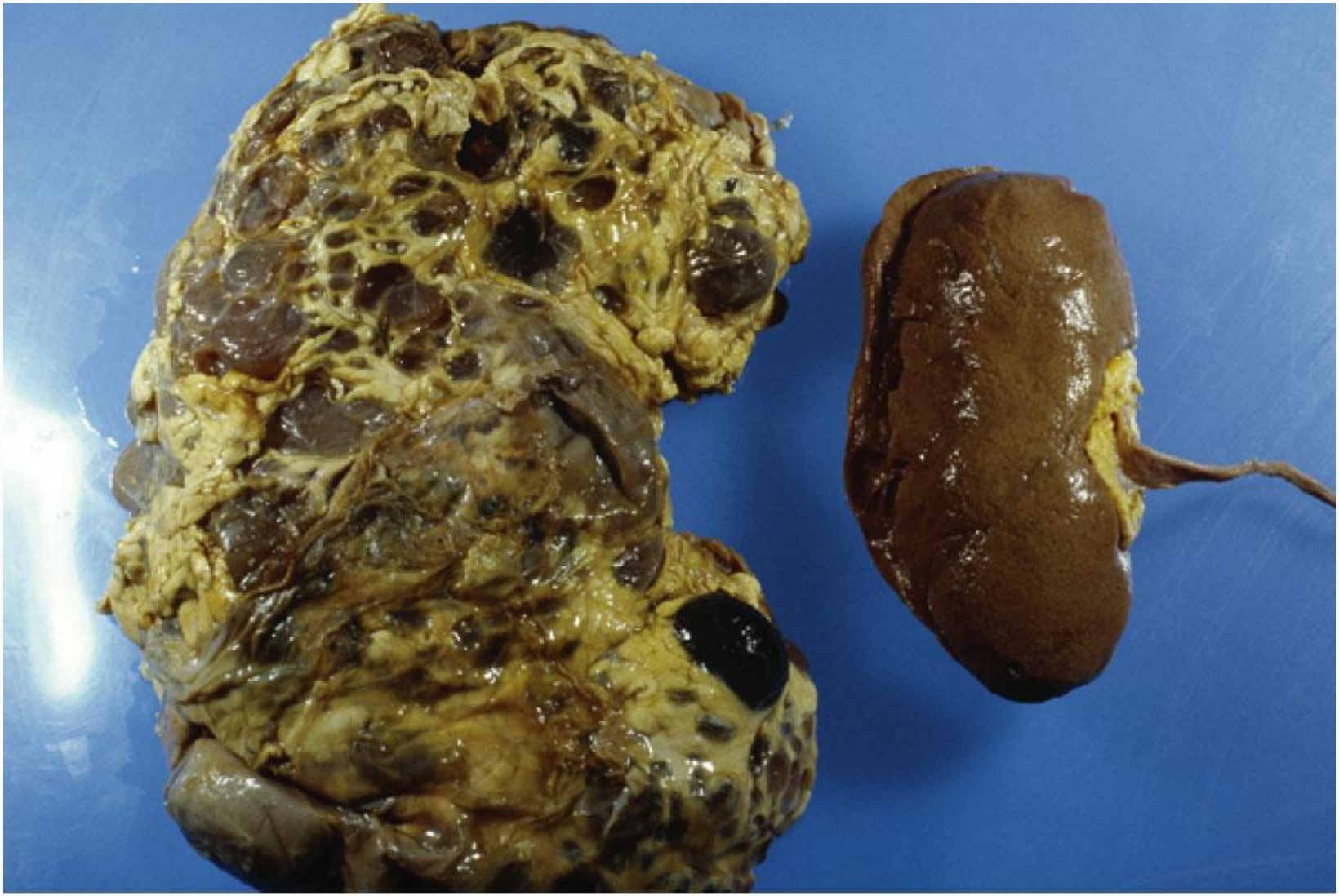
Testing available for:

- Huntington disease (HD)
- Genetic predisposition to breast cancer
- Amyotrophic lateral sclerosis (ALS)
- Polycystic kidney disease (PCKD)

Polycystic Kidney Disease (PCKD)

- Dominant trait, affects about 1/1,000
- Symptoms usually appear age ~35–50
- Formation of cysts in one or both kidneys
- Cysts grow and gradually destroy the kidney
- Treatment options are kidney dialysis or transplant, many affected individuals die

PCKD



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Newborn Screening Programs

- Mandated by law in U.S.
- Began in the 1960s with PKU testing
- Many states screen for only 3–8 disorders
- New technology screen for 30–50 disorders/ sample

Adult Screening Programs

- Not currently mandated

- Testing under certain circumstances
  - Occur mainly in defined populations
  - Tests for carriers must be available, fast, and fairly inexpensive
  - Screening must give at-risk couples several options

Tay-Sachs Disease

- Disorder that meets these conditions
- Fatal autosomal recessive trait, affects 1/360,000
- Disorder of lysosomes, leads to mental retardation, blindness, and death by age 3 or 4
- ~100x higher for Jews of Eastern European ancestry
- 1970s, carrier detection programs very successful

National Sickle Cell Anemia Control Act

- In 1972, states received funds to ID carriers of sickle cell anemia (SCA)

- Some compulsory programs required testing of all African-Americans:
  - Before attending school
  - Before obtaining a marriage license
  - Professional football players
  - Applicants to the U.S. Air Force Academy

Problems with SCA Screening Program

- In 1981, Air Force policy reversed
- Healthy carriers turned down for insurance and employment
- Lack of confidentiality and counseling

Legal and Ethical Issues

- Privacy of results extremely important
- Insurance issues
- Discrimination
- Marketing