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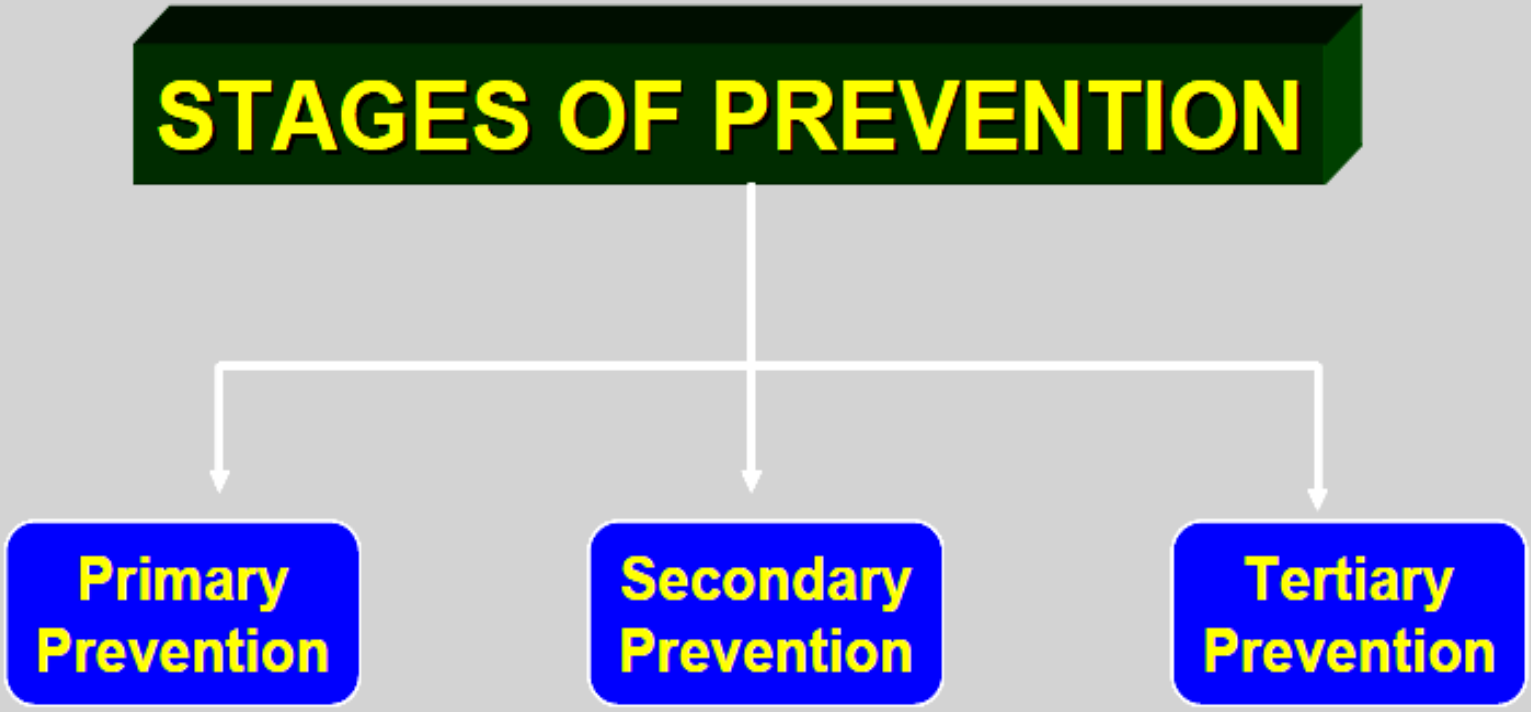
CONTROL AND PREVENTION OF GENETIC DISORDERS

MGL - 13

July 13th 2014

Control and prevention of the Diseases

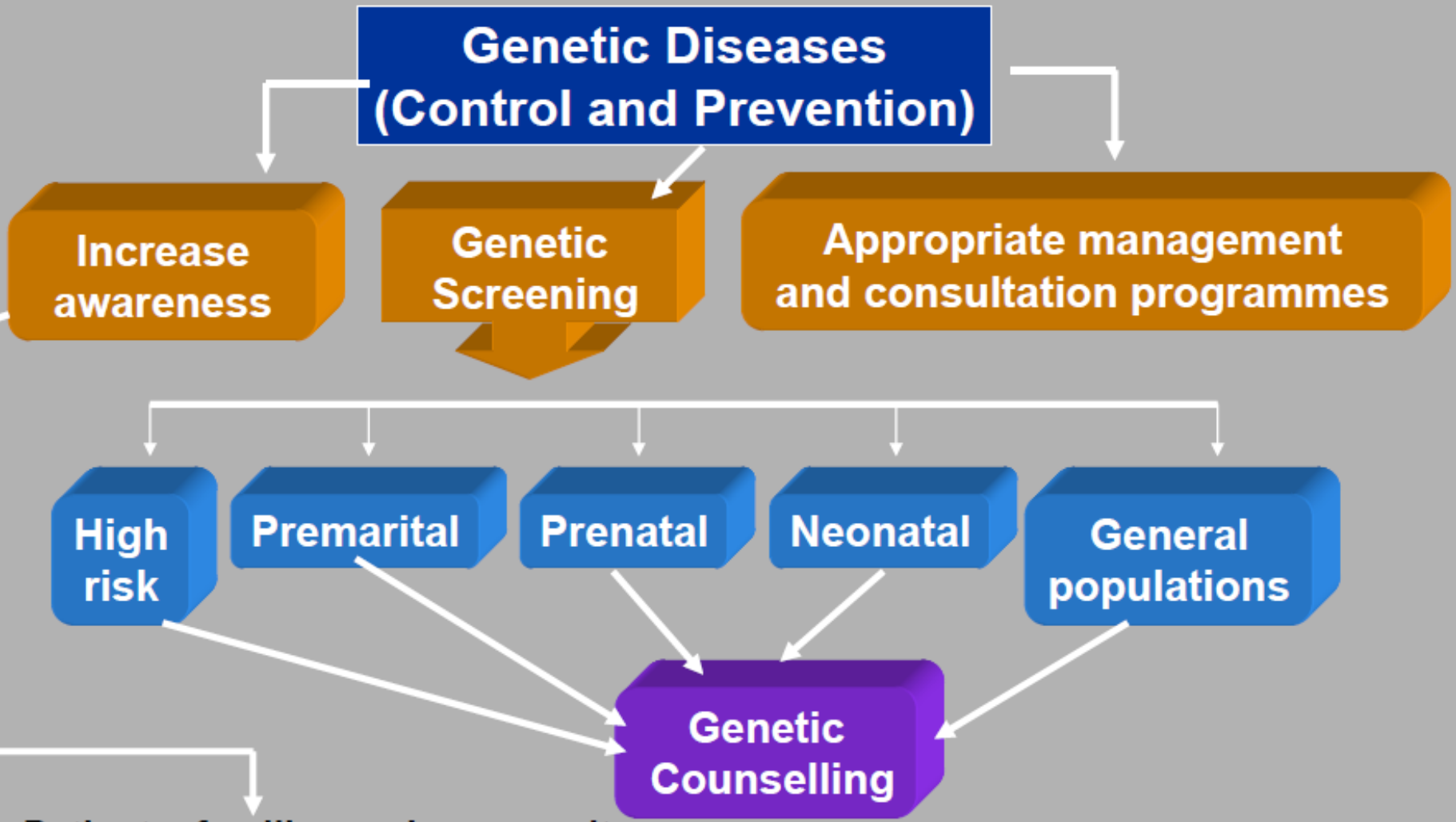
- Control and prevention programs if effectively implemented can reduce the:
  - Frequency of homozygous and double heterozygous states
  - Morbidity
  - Psychosocial trauma
- Successful implementation of control and prevention programs require awareness amongst:
  - Professionals
  - Community


STAGES OF PREVENTION
Primary Prevention
Secondary Prevention
Tertiary Prevention

Steps towards control and Prevention of Genetic Disorders

- Early detection and interaction
  - To Prevent birth of an affected child (Primary prevention)
  - To Prevent clinical manifestations in affected individuals by appropriate intervention (Secondary Prevention)
  - Provision of adequate care and rehabilitation in affected individuals (Tertiary Prevention)
- Screening
- Counseling

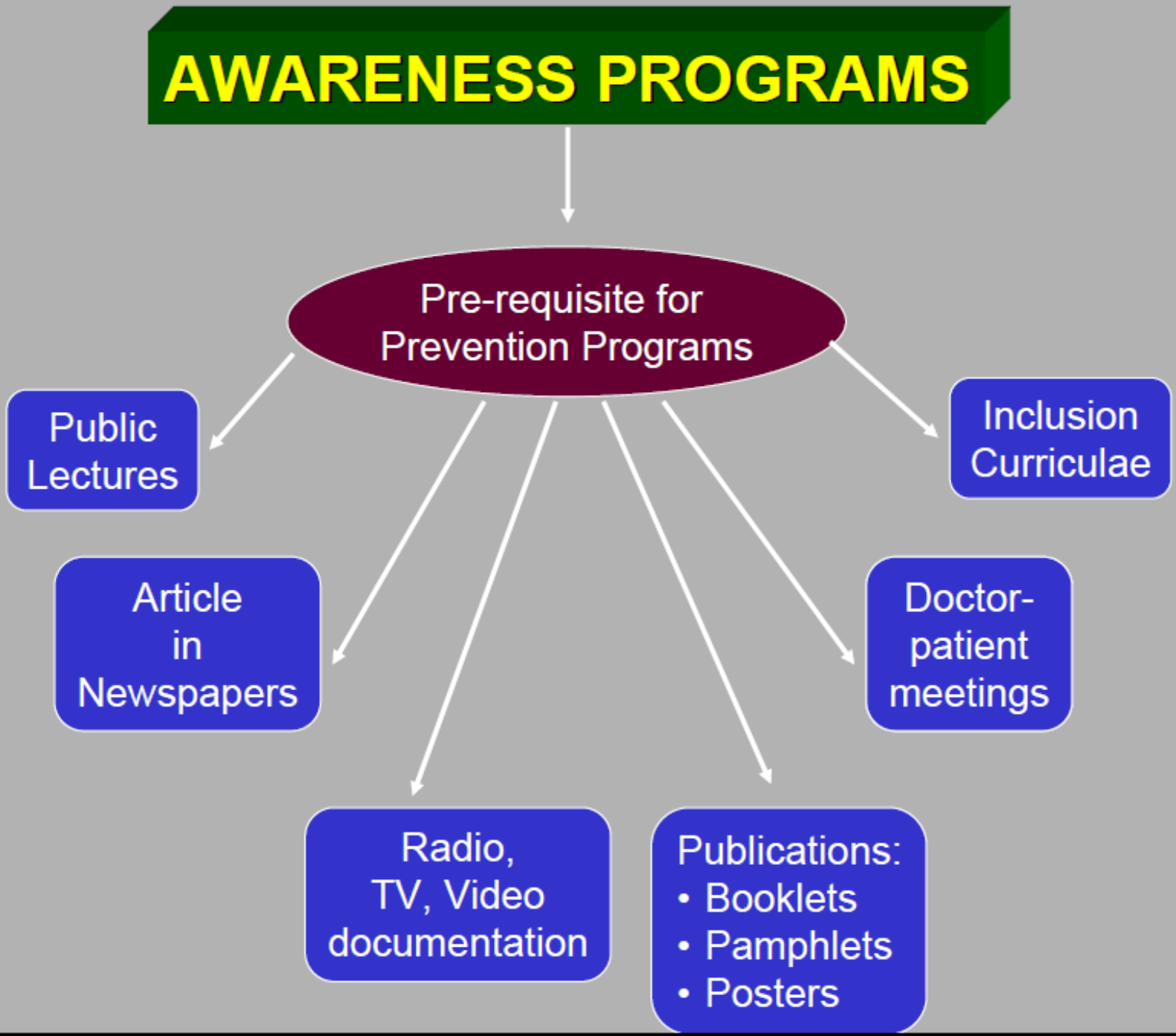
Control and Prevention Programmes For Genetic Diseases



- Patients, families and community
- Clinical staff and premedical personnels
- Health policy makers and administration

AN ESSENTIAL ELEMENT OF ALL CONTROL AND PREVENTION PROGRAMS IS:

AWARENESS


AWARENESS PROGRAMS
Pre-requisite for Prevention Programs
Public Lectures
Inclusion Curriculae
Article in Newspapers
Doctor-patient meetings
Radio, TV, Video documentation
Publications:
• Booklets
• Pamphlets
• Posters

Prevention of Genetic Disease

- Genetic counseling
- Genetic screening and testing
  - Carrier Screening
  - Neonatal screening
  - Prenatal diagnosis and selective abortion
- Premarital counseling
- Pre-implantation genetic diagnosis
- Treatment of genetic disease
- Education

Genetic Testing

Predictive testing Tells: a person if she carries a mutation that will cause, or put her at higher risk for, a disease later in life.

Newborn screening Detects: common disorders in newborns, where immediate treatment can prevent dangerous symptoms

Carrier testing Tells: a person whether or not he carries a mutation that could be passed on to his offspring. One can be a carrier, but not be at risk for a disease (as in recessive genes)

Types of Genetic Testing

1. **Carrier testing:** test family members, determine chances of having an affected child
2. **Premarital Screening**
3. **Neonatal testing:** New borne screening ID individuals for treatment
4. **Prenatal diagnosis:** determine genotype of fetus
5. **Preimplantation diagnosis (PGD):** IVF, determine genotype before transfer the fertilized ova
6. **Other Technologies**

Screening for carriers of recessive genetic diseases

The following criteria must be met

(I) Disease presentation is severe.
(ii) Screening is directed towards high risk population
(iii) Availability of an inexpensive sensitive and specific test.
(iv) Reproduction options are available to couples found to be at risk.
(v) Genetic counselling is available.

Examples of primary prevention of genetic diseases

- Carrier detection
- Premarital
- Preconception
- Preimplantation

→ Genetic Counselling → To prevent the birth of an affected child

homozygous or double heterozygous

Vaccinating the females against Rubella → Prevention of genetic defects in the fetus

Folic acid supplementation prior to and during pregnancy → Prevention of neural tube defect in newborn

Screening for presymptomatic individuals at risk for adult-onset genetic disease

- Diabetes mellitus?
- Coronary heart disease?
- Breast cancer.
- Colon cancer .
- Ovarian cancer.
- Cervix Cancer
- Prostate Cancer

Examples of screening to identify individuals with a genetic predisposition to a disease

Screening for familial hypercholesterolemia (FH)

↓

Identification of heterozygous carriers of FH
(at increased risk of premature coronary artery disease)

↓

Control of environmental factors
e.g. cigarette smoking, diet and exercise

↓

Prevention or delayed development of CAD

Premarital Screening

Conclusive counseling of identified carriers

- ⇨ Can influence marriage decision
- ⇨ Allows informed reproductive decisions
- ⇨ Marks up individuals for prenatal diagnosis
- ⇨ The ultimate goal is to reduce the birth incidence of beta-thalassemia in Jordan
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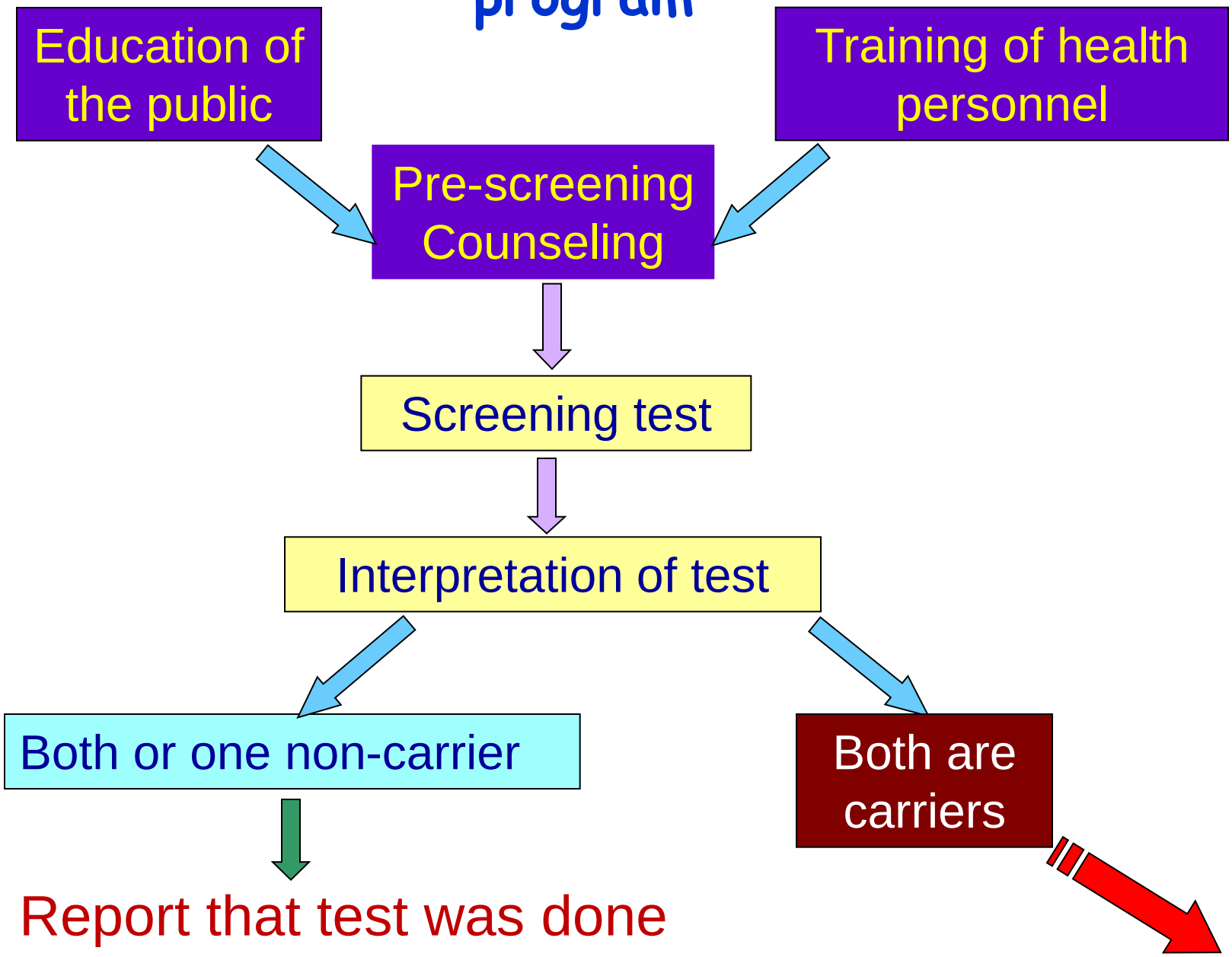
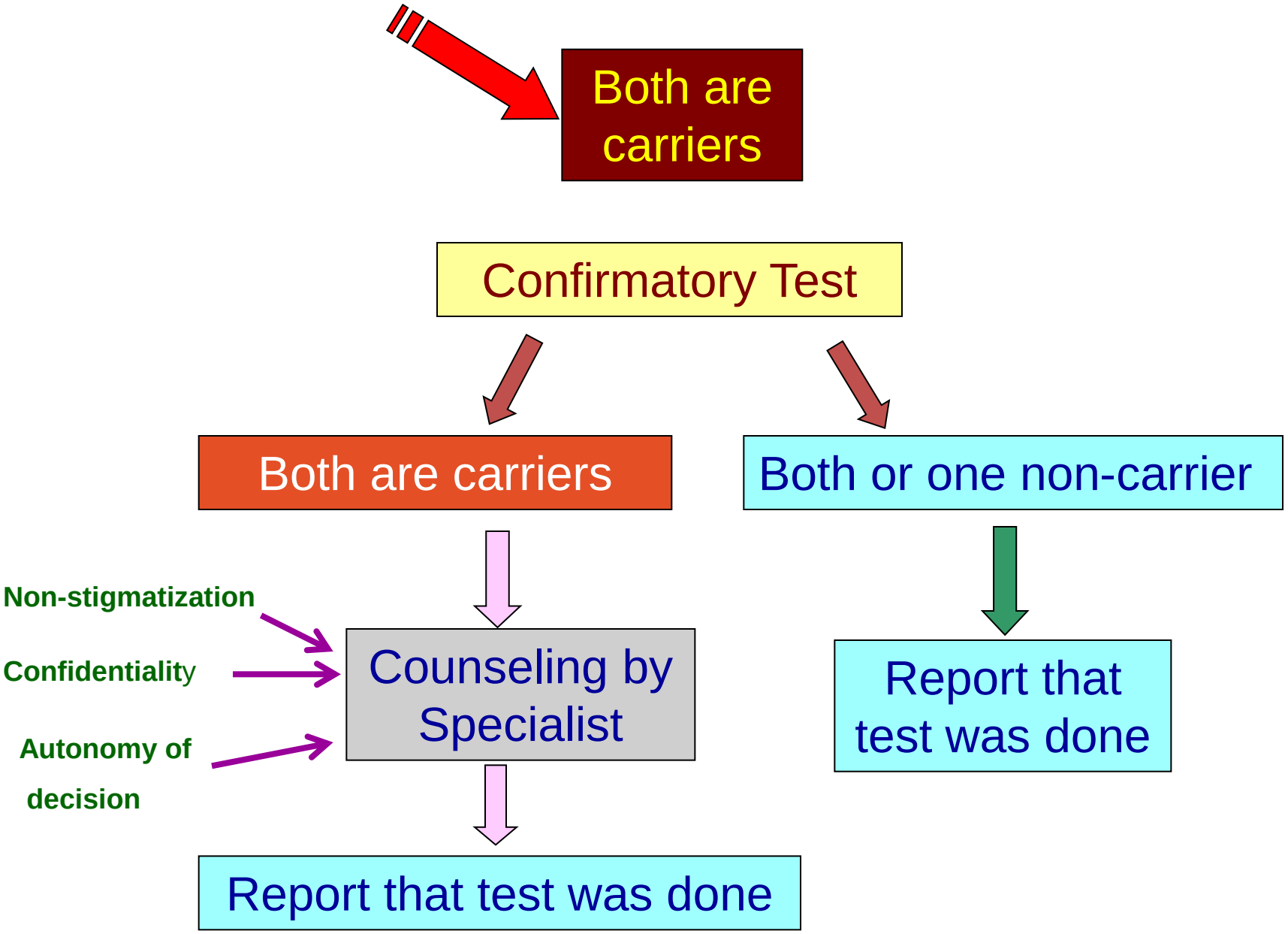
Beta-thalassemia in Jordan

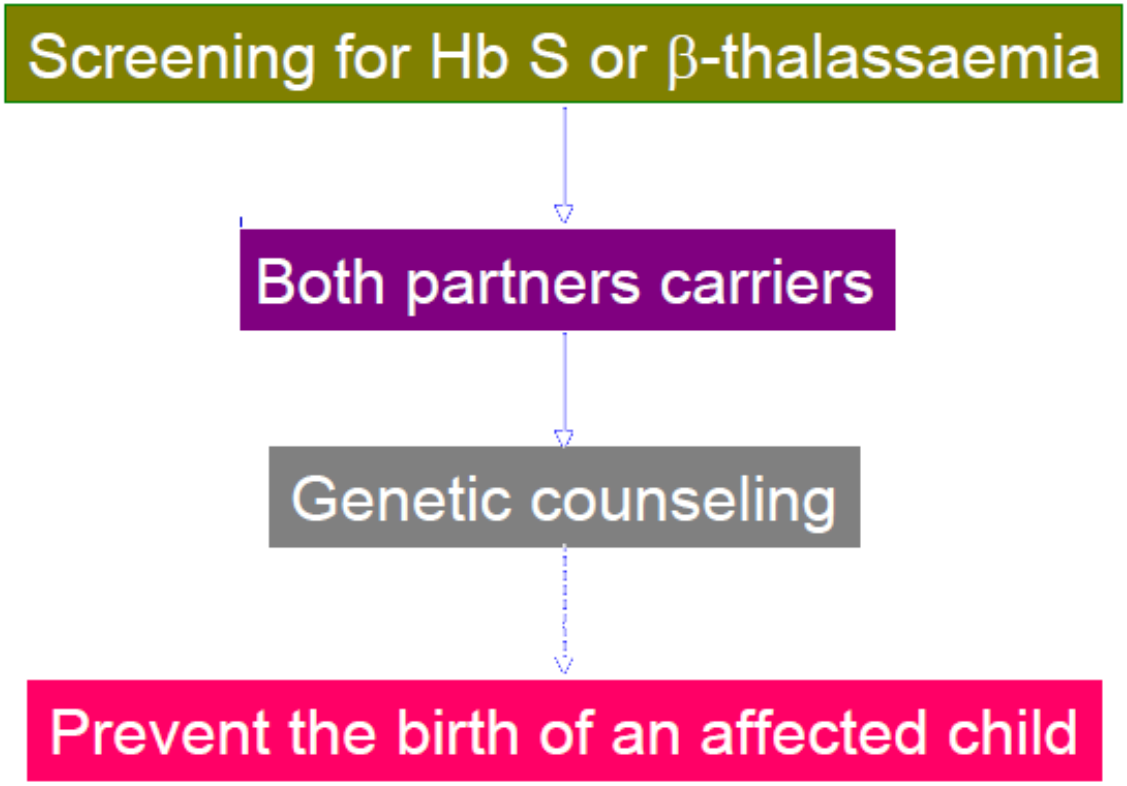
- The carrier prevalence rate of beta thalassemia in Jordan is around 4%.
- The birth incidence for beta thalassemia is about 1 in 2500 livebirths
- The registered number of beta thalassemia patients in the Kingdom is around 1200
- It is estimated that without a control program, 80-90 new cases of beta thalasemia will be born annually

Beta -thalassemia premarital screening program




Both are carriers
Confirmatory Test
Both are carriers
Both or one non-carrier
Non-stigmatization
Confidentiality
Autonomy of decision
Counseling by Specialist
Report that test was done
Report that test was done

Examples of screening to identify individuals at increased risk of having children with genetic diseases



Successful Programs

- **Screening programs for β-thal.**
  - **In Greece and Italy have resulted in a drop in the incidence of affected homozygotes by almost 95%.**
  - **In Cyprus almost to100%**

Premarital Screening for β-thalassaemia in Cyprus

The success of a genetic screening program can be judged on the basis of a reduction in the births of affected babies.

In 1974:	Birth incidence of β-thal. major = 1 in 250.
	Introduction of a comprehensive screening program to determine carrier status of young adults and premarital couple.
1984:	Incidence of affected babies declined by over 95%.
1990's:	No new birth of a β-thal. major baby.

NEONATAL SCREENING

- Disorder produces irreversible damage before onset of symptoms
- Treatment is effective if begun early
- Natural history of disorder is known

The Cardinal Principles of Screening

Some of the basic criteria for determining which inherited disorders for newborn screening include:

- The disorder has a relatively high incidence so that the cost per diagnosed individual is reasonable
- An effective and not overly expensive treatment is available
- A relatively inexpensive screening test is available that is suitable for high volume testing (preferably automatable)
- The screening test has a very high sensitivity (i.e. a very low rate of false negatives) and high specificity (i.e. low rate of false positives which require expensive follow-up)
- Diagnostic Urgency
- Government Mandate

Why do Newborn Testing?

- Reduce mortality and morbidity of inherited disease
- Identify congenital disorders
- Improve patient outcomes through early detection and treatment
  - Minimizing the impact of disease
  - Offering essentially a "normal" life
- Offer a cost benefit to society

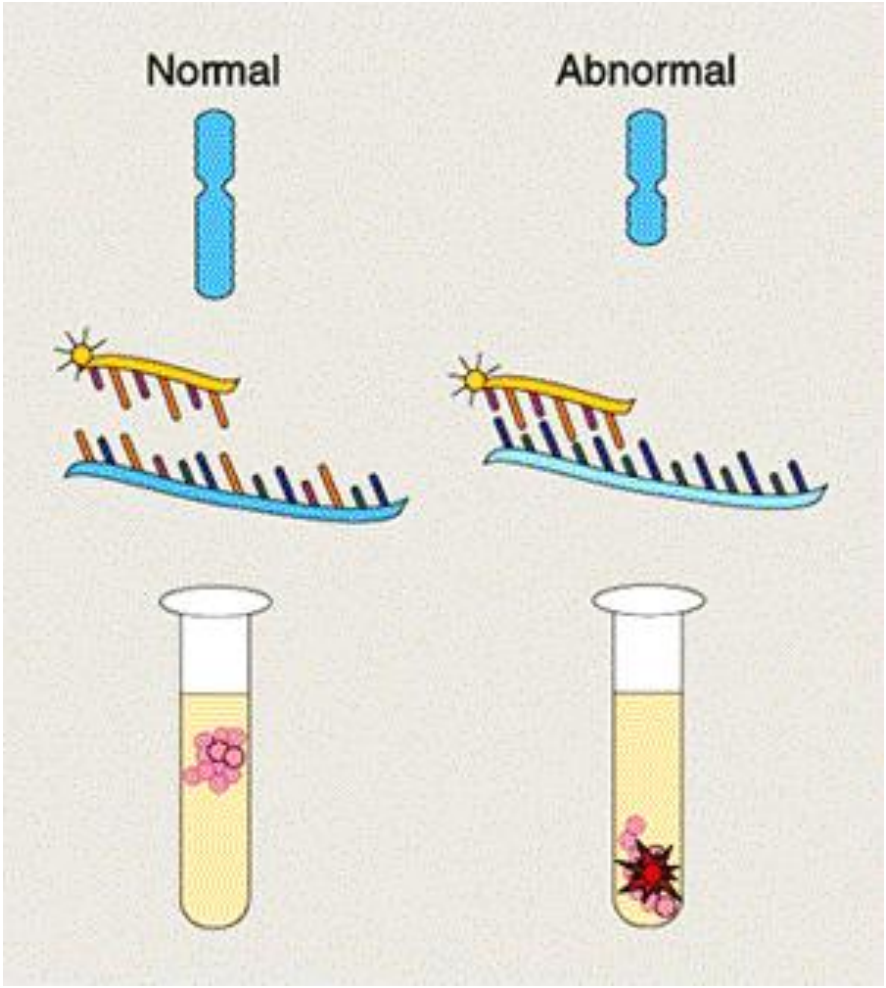
Conditions for Which Neonatal Screening Can be Undertaken

Disorder	Test/method
Phenylketonuria	**Guthrie" or automated fluorometric assay**
Congenital hypothyroidism	**Thyroxine or thyroid stimulating hormone**
Other inborn errors	
Biotidinase deficiency	Specific enzyme assay
Galactosaemia	**Modified Guthrie**
Homocystinuria	Modified Guthrie
Maple syrup urine disease	Modified Guthrie
Tyrosinaemia	Modified Guthrie
Miscelaneous	
Congenital adrenal hyperplasia	17-Hydroxyprogesterone assay
Cystic fibrosis	Immunoreactive trypsin and DNA analysis
Duchennemuscular Dystrophy	Creatine kinase .
Sickle-cell disease,	Hemoglobin electrophoresis

Newborn Screening Programs

Types of Genetic Tests

1. Cytogenetic
2. DNA
3. Metabolic



PRENATAL SCREENING

Prenatal Screening in High Risk Group

To identify affected fetus

Termination of pregnancy

Before 120th day → Acceptability of termination?

- Genetic counselling to prepare the couple psychologically.
- Preparation for adequate management and care of affected child.

Indications for prenatal diagnosis:

- Advanced maternal age
- Previous child with a chromosome abnormality
- Family history of a chromosome abnormality
- Family history of single gene disorder
- Family history of a neural tube defect
- Family history of other congenital structural abnormalities
- Abnormalities identified in pregnancy
- Other high risk factors (consanguinity, poor obst., history, maternal illnesses)

Indications for Prenatal Diagnosis

- High Genetic Risk
- Sever Disorder
- Treatment not available
- Reliable Prenatal Test
- Termination Pregnancy Acceptable

Methods of prenatal diagnosis

Non-invasive

- Maternal serum AFP
- Maternal serum screen
- Ultrasonography
- Isolation of fetal cells /DNA from maternal circulation

Invasive:

- Amniocentesis
- Chorionic villus sampling
- Cordocentesis
- Fetoscopy
- Preimplatation genetic diagnosis

list of some of the more common genetic diseases that can be detected. Any gene disorder in which the DNA base pairs or code is known, can be detected by PND & PGD.

- Alpha-thalassemia
- Glycogen storage disease
- Beta-thalassemia
- Hemophilia
- Canavan's disease
- Huntington's diseaseCystic fibrosis
- Marfan's syndrome
- Charcot-Marie-Tooth disease
- Myotonic Dystrophy
- Down's syndrome
- Neurofibromatosis
- Duchenne muscular dystrophy
- Polycystic Kidney Disease
- Fanconi anemia
- Retinitis pigmentosa
- Fragile X syndrome
- Spinal Muscular Atrophy
- Gaucher disease
- Tay Sachs disease

Non Invasive Procedures

Maternal Serum Alpha Fetoprotein (AFP)

- Major protein produced in the fetus
- Elevated levels with open neural tube defect in the fetus
- Second most common fetal malformation
- Maternal serum testing done between 15-22 weeks of gestation

Second Trimester Maternal Serum Screening for Aneuploidy

- Performed at 15-20 weeks
- Singleton gestation
- Adjusts age risk based on levels of
  - **AFP**
  - **hCG**
  - **Unconjugated esteriol (uE3)**
  - **Inhibin-A**

  "Triple" (AFP, hCG, uE3)

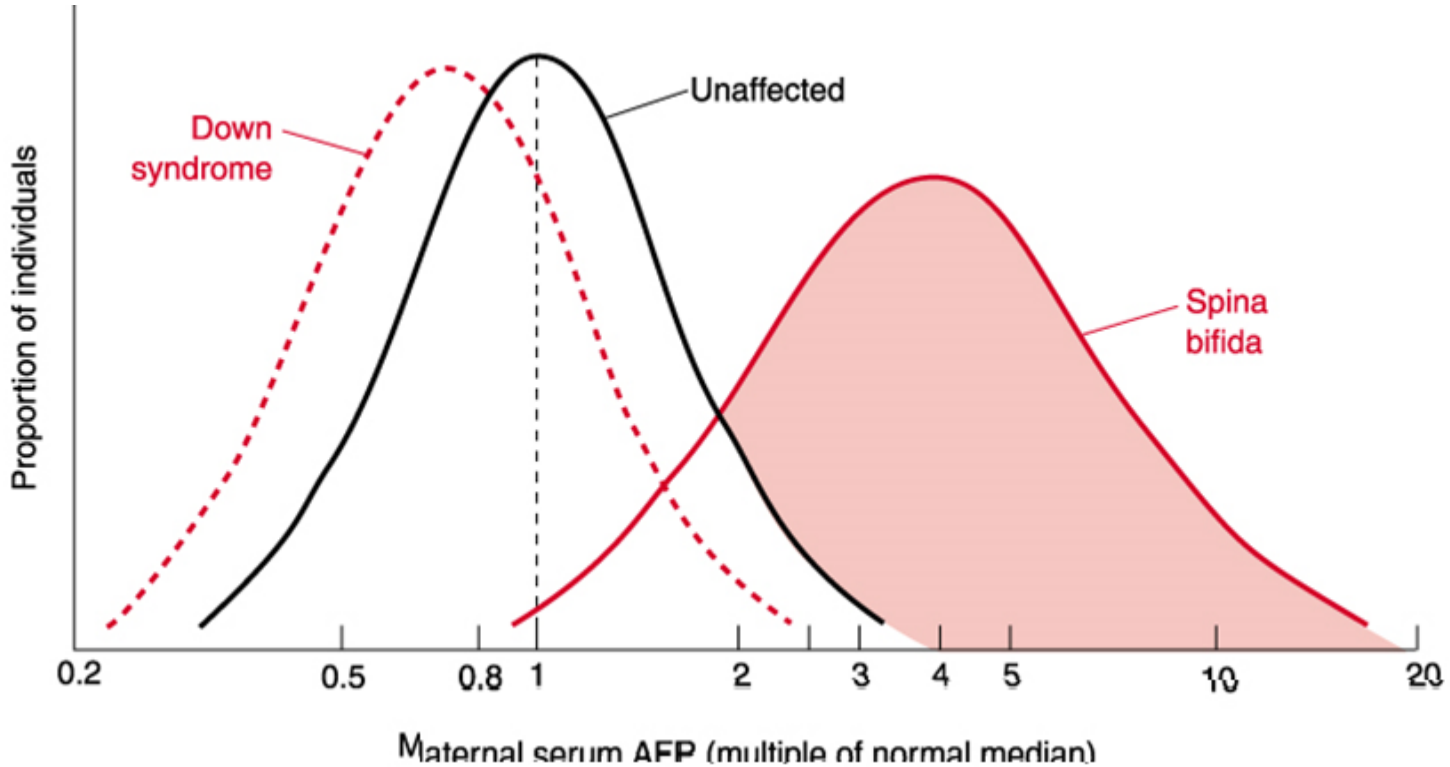
  "Quad" (AFP, hCG, uE3, Inhibin-A)
- Detection rate in women
  - **<35: 60-75% for DS**
  - **>35: 75% or more**
  - **>80% for trisomy 18**
- Positive screening rate 5%

Extra Note Added To The Previous Slides

The second trimester screen as we know it today consists of 3 or 4 markers that can be measured between 15 and 20 weeks gestation and is referred to as the triple or quad screen. A triple screen includes … A quad screen includes inhibin-A. The detection rates are …

Combined use of MSAFP and ultrasound approach the accuracy of AFAFP

In many prenatal diagnosis programs, first or second degree relatives of patients with NTDs may have an MSAFP assay at 16 weeks followed by detailed ultrasound at 18 weeks



Elevated AFP

- Multiple gestation
- Fetal demise, premature delivery, growth retardation
- Abdominal wall defect
- Congenital nephrosis
- Maternal liver disease

Emerging Technologies

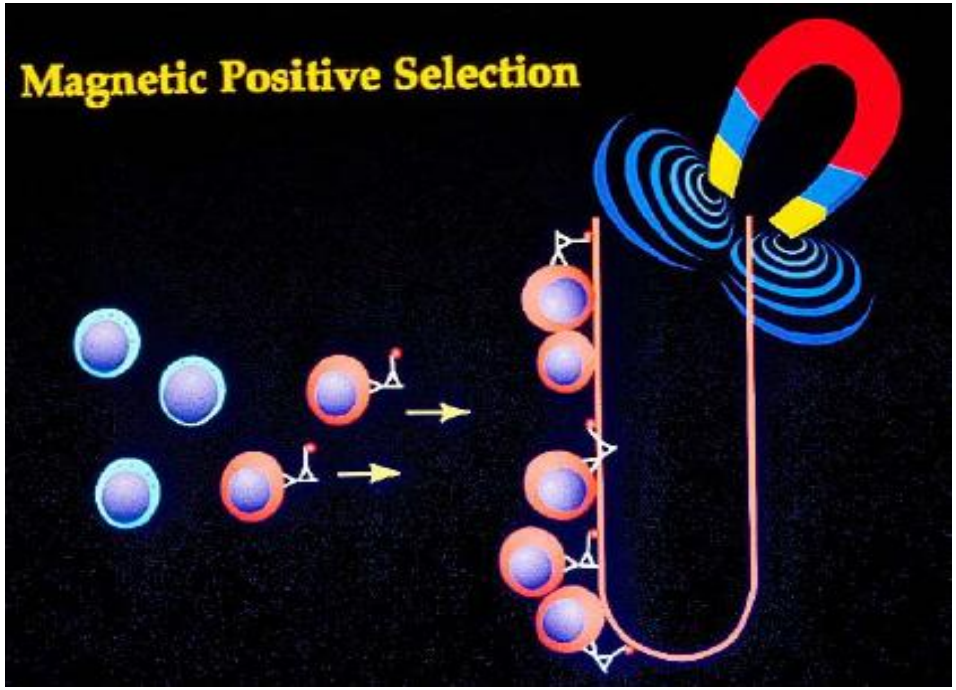
Cell & Cell-Free Fetal DNA Sampling

Timeframe: As early as 6-8 weeks post-LMP

- Very small number of fetal cells migrate into the mother's circulation – 1 out of 10^7 nucleated cells
- Techniques have been developed to isolate these cells from the maternal blood and tested diagnostic purposes
- At this time, still in developmental stages
- Fetal cells may remain in circulation for years
- In addition, cell-free fetal DNA is found in maternal circulation – this may prove easier to isolate and to test than the fetal cells

Other Sources of fetal tissues for Non-Invasive Prenatal Diagnosis

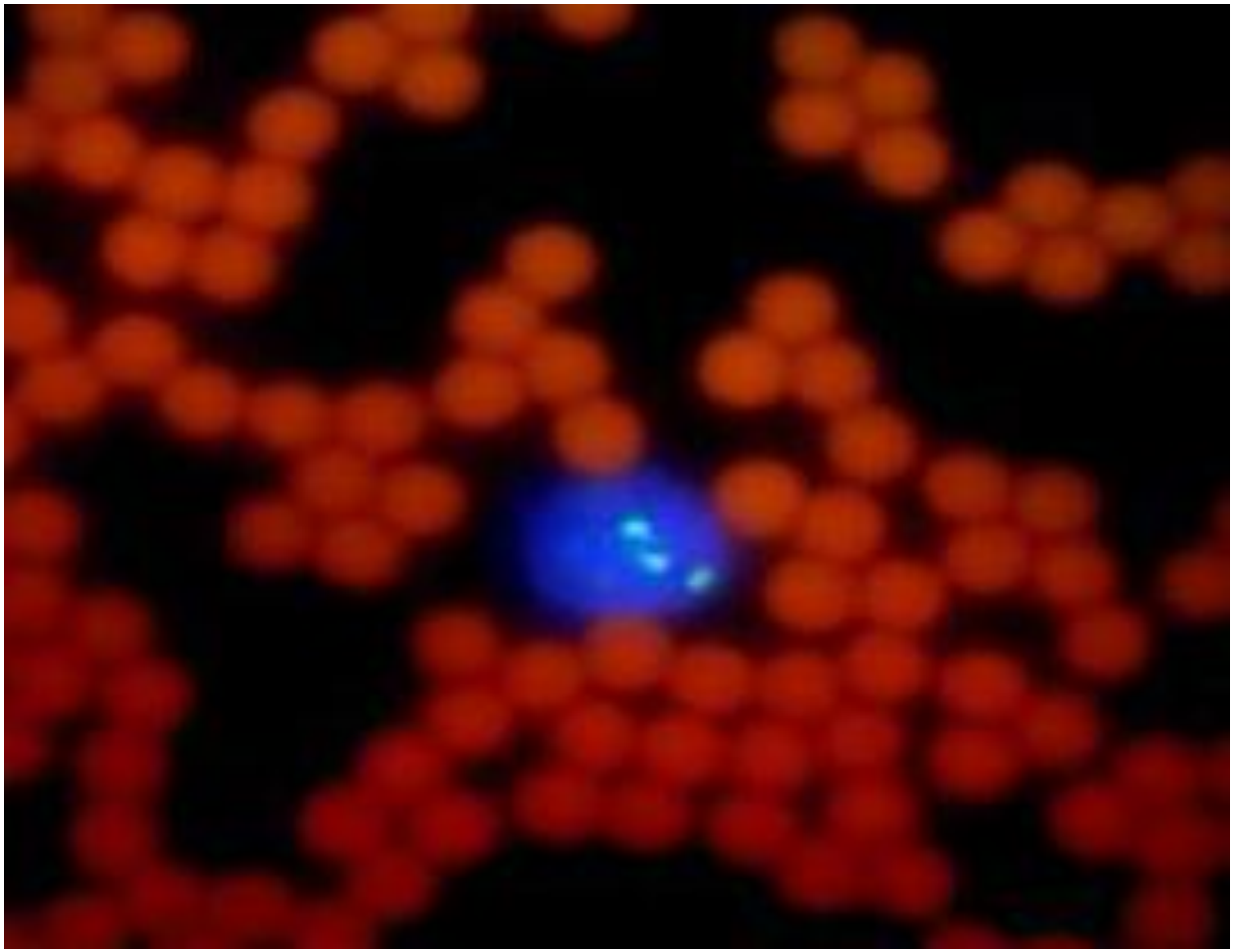
- **Fetal Cells in maternal circulation**
  - Erythrocytes
  - Trophoblastic Cells
  - Leukocytes
    - ✓ Difficult to Isolate
    - ✓ Very low abundance
    - ✓ Persist for years after delivery



Very small number of fetal cells migrate into the mother's circulation
1 out of 10^7 nucleated cells

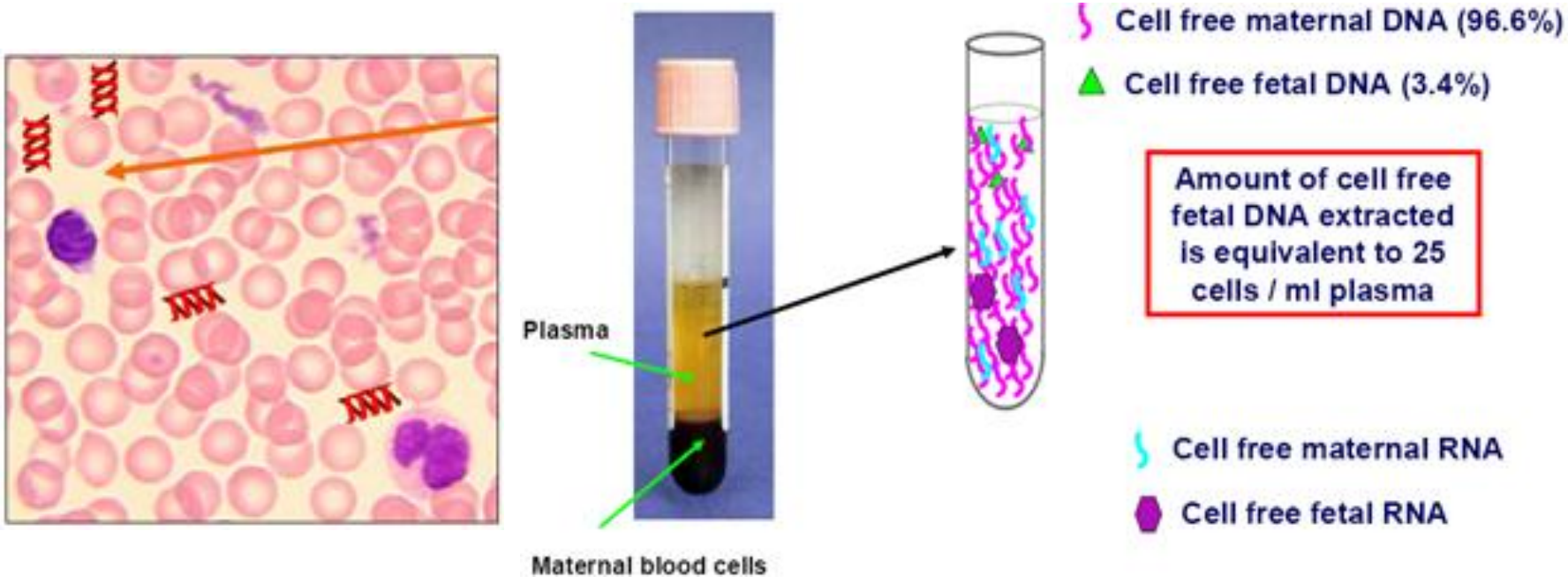
Sorting using CD-71 (transferrin receptor to separate nucleated red blood cells.
FISH –for X and Y Signals

Fetal Cells in Maternal Blood



Cell free fetal nucleic acids from maternal plasma

- 1977: Small quantities of free DNA observed in cancer patients
- 1997: Cell free DNA isolated from the plasma of pregnant women



What are cell free nucleic acids

Cell free fetal DNA (cffDNA)

- cff DNA can be detected in plasma of pregnant woman
- cff DNA only makes up about 5% of total cell free DNA extracted most common from the mother
- cff DNA derived from the placenta
- Can be detected as early as 5 weeks of gestation
- Rapidly cleared after delivery

Cell free fetal RNA (cff RNA)

- cff RNA can be detected in plasma of pregnant women
- cfRNA can be fetal specific maternal specific or expressed in both fetus and mother blood
- Can be detected early in pregnancy
- Rapidly cleared after delivery

How good is Non-Invasive Prenatal Testing?

- **Moving target**
- **Currently literature is primarily from companies or those holding patents**

	Overall ranges		
	T21	T18	T13
Specificity (%)	99-100	99-100	99-100
Sensitivity (%)	98-100	97-100	79-100
Positive Predictive Value [PPV] (%)	90-95*	84*	52*
Negative Predictive Value [NPV] (%)	99.9	99	100

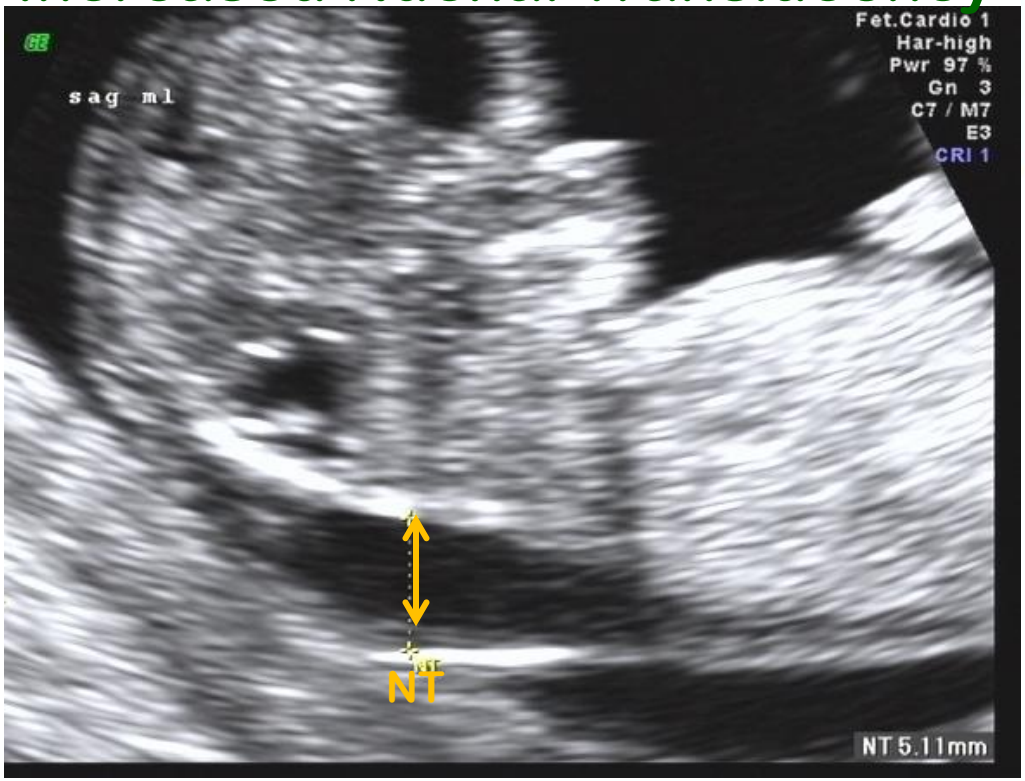
*ASHG Oct 2013 platform presentation – data from BGI China; 63,543 pregnancies

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

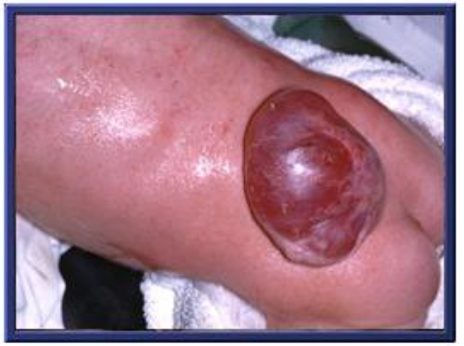
ULTRASOUND

Increased Nuchal Translucency



Anencephaly

spina bifida



NT measurement	Chance of normal birth
≤ 3.4mm	95%
3.5 – 4.4mm	70-86%
4.5 – 5.4mm	50-77%
5.5 – 6.4mm	67%
≥ 6.5mm	31%

Trisomies 21, 18, 13, triploidy and Turner syndrome

NT ≥ 3 mm is ABNORMAL

Invasive Procedures

Amniocentesis

Timeframe: 15-17 weeks post-LMP (Can be done at 10-14 weeks)

20-30 ml amniotic fluid is collected transabdominally or transcervically with a needle - contains supernatant & fetal cells.

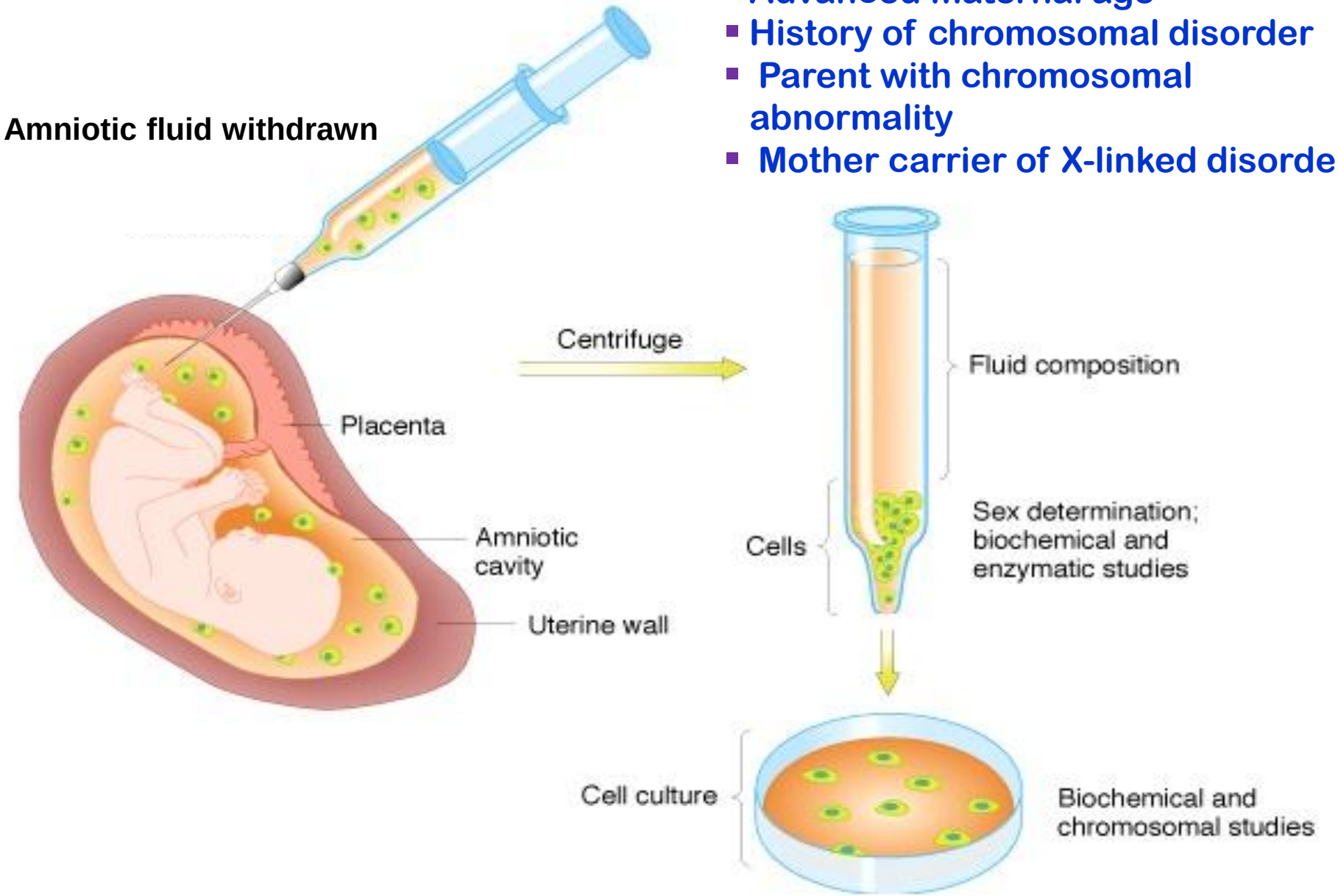
Cells cultured & examined for chromosome structure/number and/or direct DNA testing

The amniotic fluid is analyzed for AFP levels

Amniocentesis

Used when

- Advanced maternal age
- History of chromosomal disorder
- Parent with chromosomal abnormality
- Mother carrier of X-linked disorder



Amniocentesis

Advantages:

- Can examine AFP levels for spinal defects
- Can be performed by an Ob/Gyn vs. perinatologist
- Fetal loss rate very low (0.5%) - for late Amniocenteses

Disadvantages

- Early amniocentesis has a higher risk of miscarriage (5%)
- Longer wait time for patients than CVS – 1-2 weeks
- Also have some risk of mosaicism

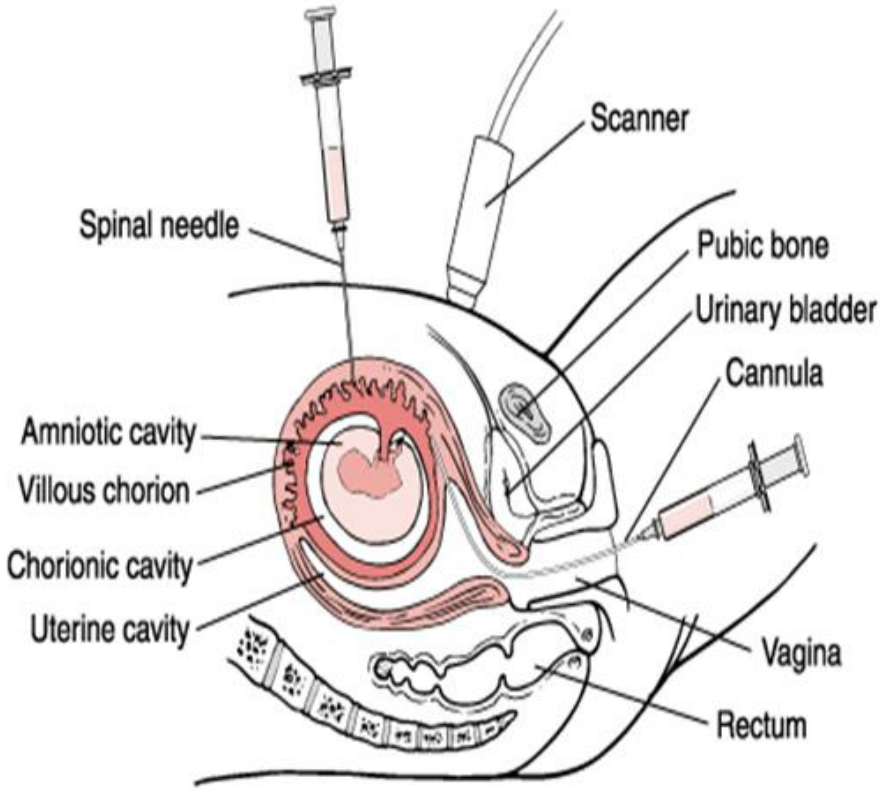
Invasive Testing
Chorionic Villus Sampling (CVS)

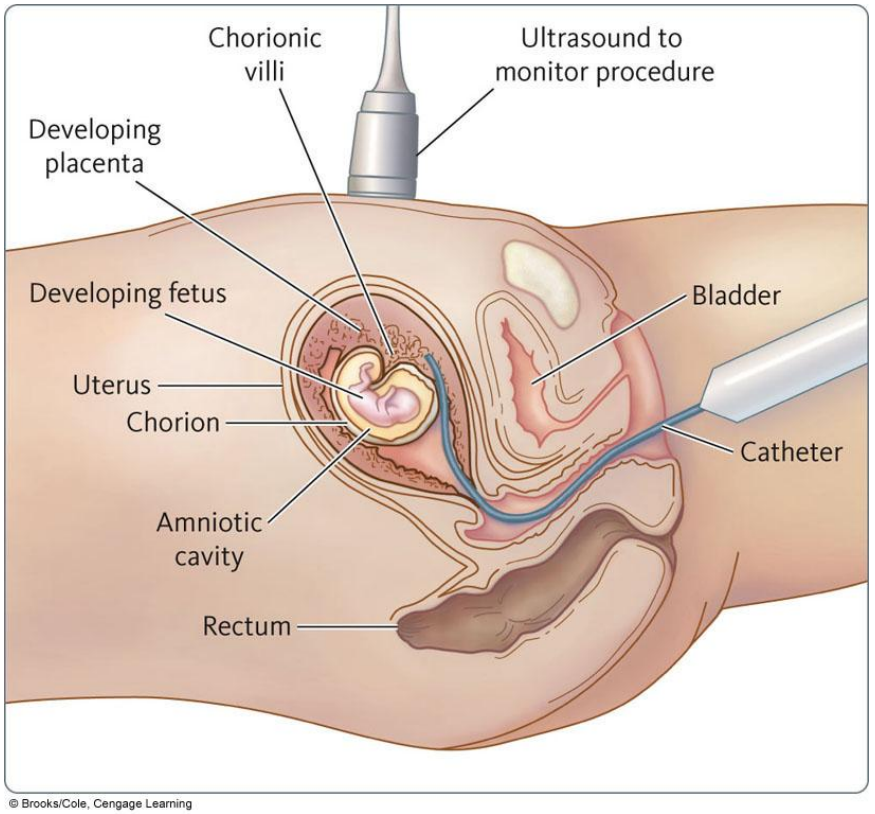
Timeframe: 8-10 weeks post-LMP

- Essentially a placental biopsy
- Tissue biopsy from the villous area of the chorion is aspirated transcervically or transabdominally

Cells are cultured and analyzed either for chromosomes or direct DNA mutations or direct assays for biochemical activity

Review of CVS Procedures





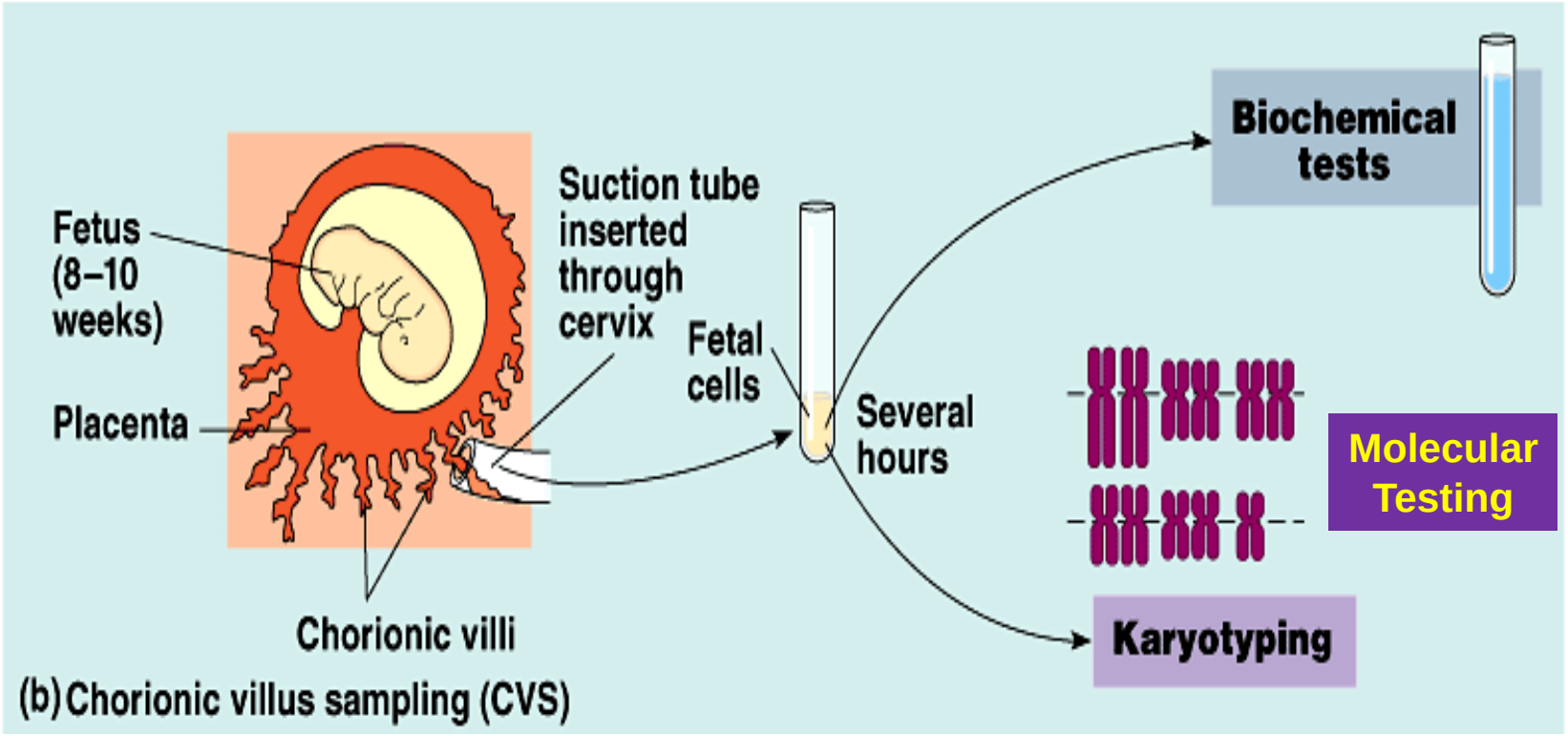
Chorionic villus sampling (CVS)

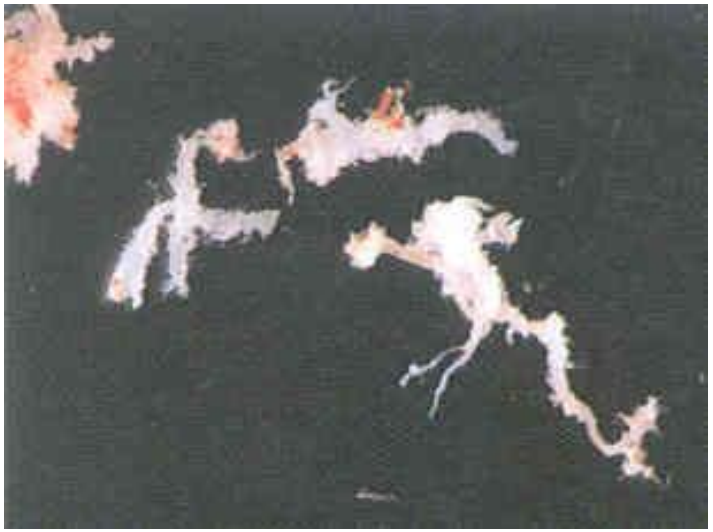
Advantages:

- first trimester diagnosis
- diagnostic results provided
- 99% of the time
- post-CVS fetal loss rate low (1%)
- results usually obtained in 5-7 days

Disadvantages

- looks only at extraembryonic material - will not detect a defect arising after embryonic material partitioned off
- confined placental mosaicism may be a problem (2%)
- only gathers cells, not fluid - can't measure AFP
- **Can't identify NTDs**





Chorionic Villus Material

Cordocentesis

Timeframe: 19-21 weeks post-LMP

Advantages:

- Rapid diagnosis time, fetal blood cells only need to be cultured for a few days to provide good chromosomes

Disadvantages

- Must be performed by a perineonatologist because of difficulty in accessing the umbilical vein
- Higher fetal loss than with CVS or Amnio (2-3%)

Fetoscopy

Timeframe: 15-18 weeks post-LMP

Structural abnormalities, skin bx for (epidermolysis bullosa)

Invasive prenatal diagnostic methods

Technique	Timing	Miscarriage risk	Applications
Chorionic villus sampling	11–14 weeks	~ 1 %	– chromosome analysis (karyotyping) – molecular genetic diagnosis – biochemical diagnosis
Amniocentesis	15–17 weeks	0.5 %–1 %	– chromosome analysis – diagnosis of open neural tube defects – molecular genetic diagnosis – biochemical diagnosis
Placental biopsy	From 15 weeks	~ 1%	– chromosome analysis – molecular genetic diagnosis – biochemical diagnosis
Cordocentesis	from 16–20 weeks *1	~ 1 %	– chromosome analysis – hematological and biochemical diagnosis
Fetal biopsy	from 20 weeks	*2	– diagnosis of specific genetic dermatoses

Prenatal Diagnosis

What technique do you use?

Depends upon what you are looking for

- Chromosomal abnormalities - need to look at chromosomes - need live fetal cells obtained from amniocentesis or chorionic villus sampling
- Hormone or enzyme levels - need cells or fluid
- Direct mutation analysis - need DNA (fetal cells)
- **Tests: Karyotyping, FISH, CGH, Molecular, Biochemical**

Preimplantation Genetic Diagnosis (PGD)

Pre-implantation Genetic Diagnosis (PGD)

What is it?

Genetic analysis of a single cell from an eight-cell embryo done in conjunction with in vitro fertilization (IVF) to improve the chances of a “normal” pregnancy.

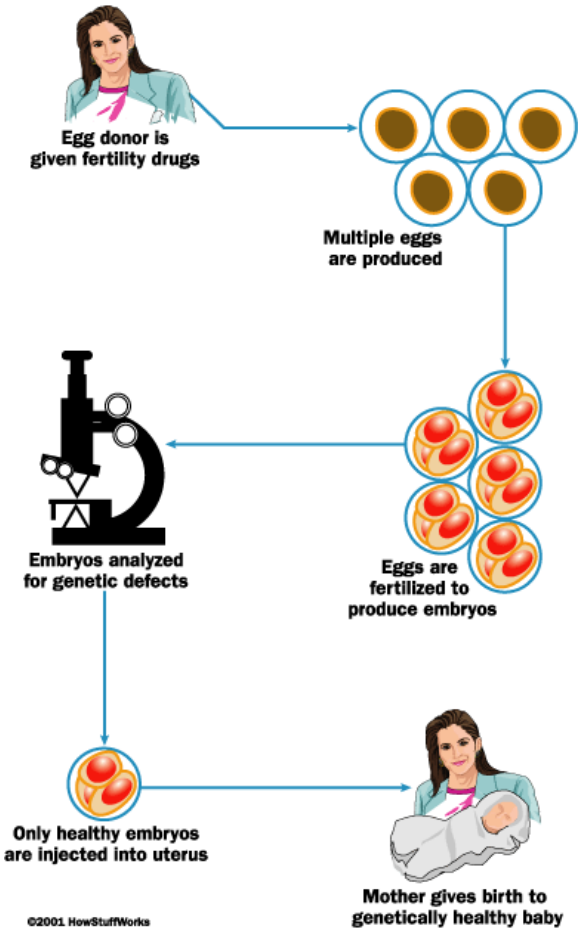
Preimplantation genetic diagnosis (PGD)

- Introduced in 1990 by Verlinsky et al in Chicago with polar body biopsy
- In London by Handyside et al that same year with blastomere biopsy
- **Indications**: expanded rapidly

➔Conceive with healthy embryos tested in vitro before implantation → avoid the dilemma of whether or not to terminate a pregnancy or deliver a sick child

PGD Process

- Ovulation Induction
- Retrieval
- Fertilization
- Embryo Bx on Day-3
- Genetic Analysis
- Embryo Transfer



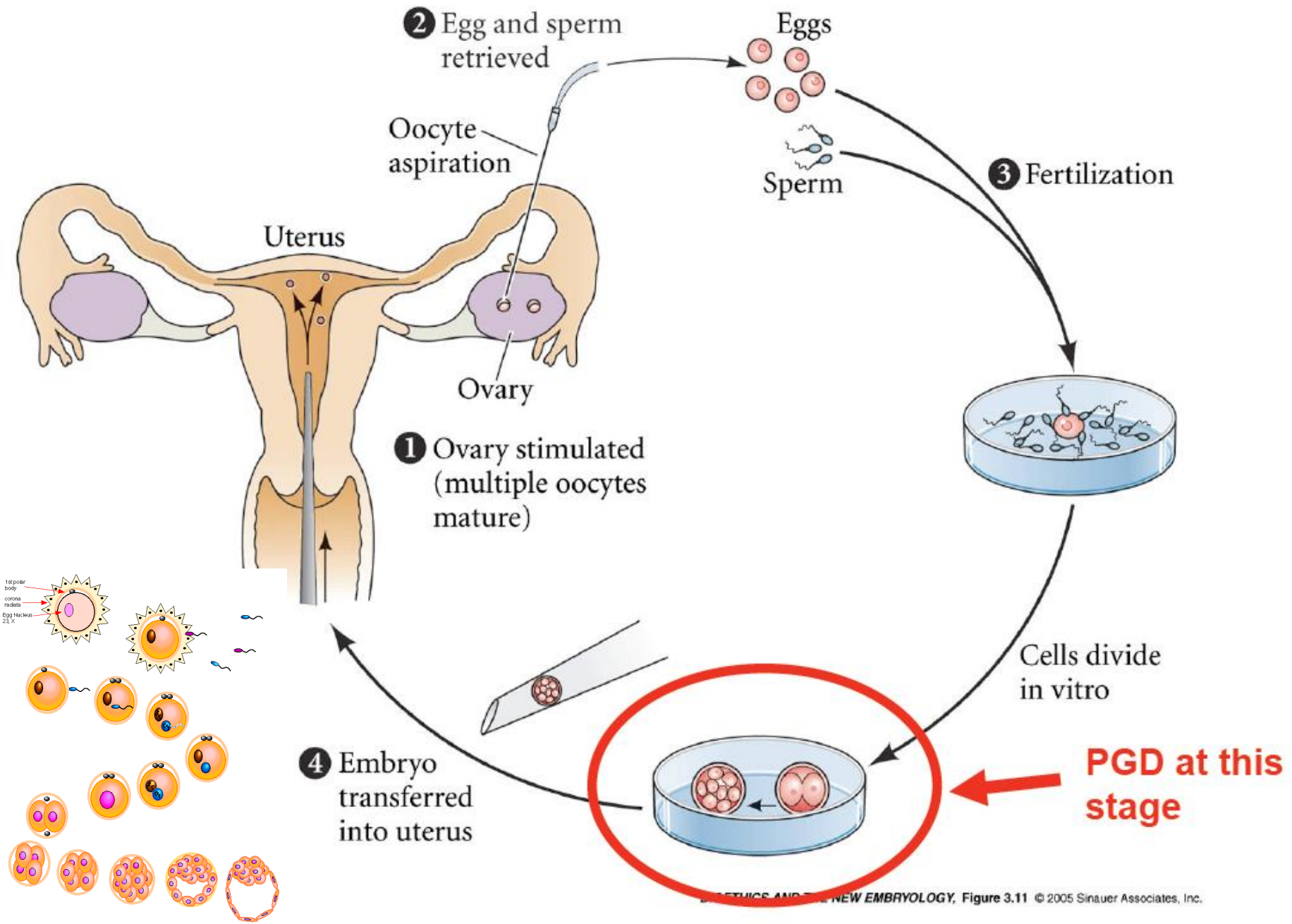
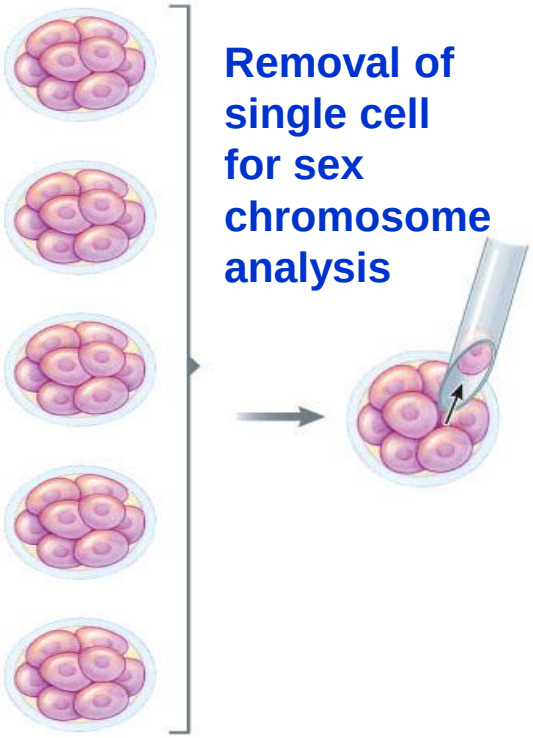


Figure 3.11 © 2005 Sinauer Associates, Inc.

Preimplantation Genetic Diagnosis (PGD)

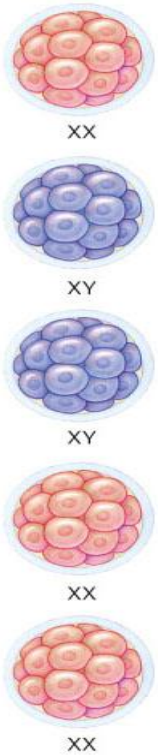
Eight-cell embryos



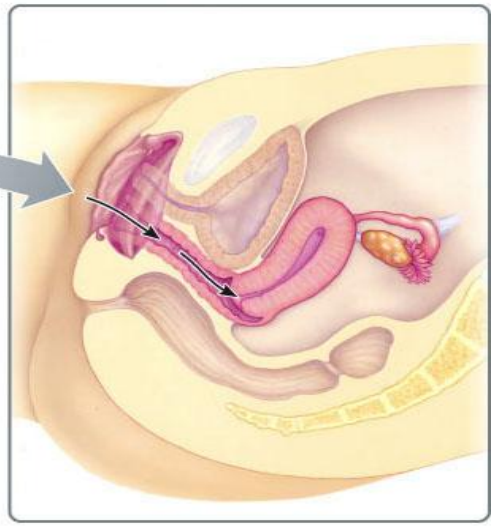
Removal of single cell for sex chromosome analysis

Single cells

Embryo



Transfer of selected embryos to patient



1) Eggs are removed from the ovary, fertilized, and grown to the eight-cell sta

2) Single cells are identified as either male or female.

3) Embryos of the desired sex are selected.

4) The selected embryos are transferred to the uterus for development.

- Ovarian stimulation for IVF with PGD
- Embryo micromanipulation
- Technique used for biopsy
- Numbers of cells removed from the embryo

➔ May affect :

- ➔ Embryo development,
- ➔ Implantation rate,
- ➔ The pregnancy outcome

PGD may now be offered

- All known single-gene disorders
- Chromosomal rearrangement
- HLA-matched siblings
- Cancer predisposition genes
- Late-onset disorders
- Monogenic disorders
- Translocations together with aneuploidy
- Couple who carry a genetic disorder

PGD for HLA Typing

- ✓ "Savior siblings": International controversy
- ✓ Matched **H**ematopoietic **S**tem **C**ell **T**ransplantation:

  Donate cord blood or bone marrow

  - **Nonmalignant disorders**
    - Genetic diseases affecting the hematopoietic and/or the immune system: *(Thalassemia, Fanconi anemia, Wiskott-Aldrich syndrome, sickle-cell disease)*
    - Acquired diseases like aplastic anemia
  - **Malignant diseases** like leukemia (↓ Post-transplant morbidity/mortality rates)

HLA Tissue Typing Saviour Siblings

Molly and Adam Nash
Fanconi Anaemia

Zain Hashmi
Beta thalassaemia

Charlie Whitaker
Diamond Blackfan
Anaemia

Preimplantation Genetic Diagnosis (PGD)

Advantages:

- Very early diagnosis
- Only transfer unaffected (or carrier) embryos

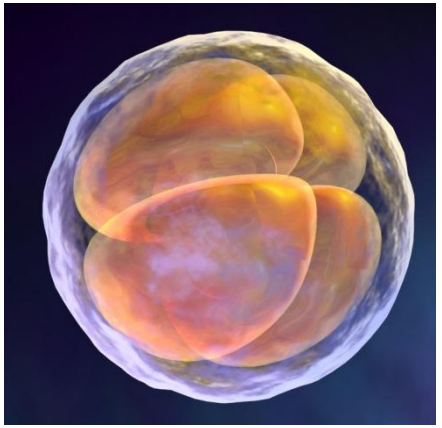
Disadvantages

- Cost is extremely high
- "Success"/implantation rate low
- Discard affected or unused embryos,
  - which has raised ethical concerns

PGD Indications

Procedure is offered to couples:

- With known ***single gene disorders*** that can be detected by PGD
- With known *chromosomal abnormalities* that can be detected by PGD
- Requesting sex selection for *X-linked disorders*

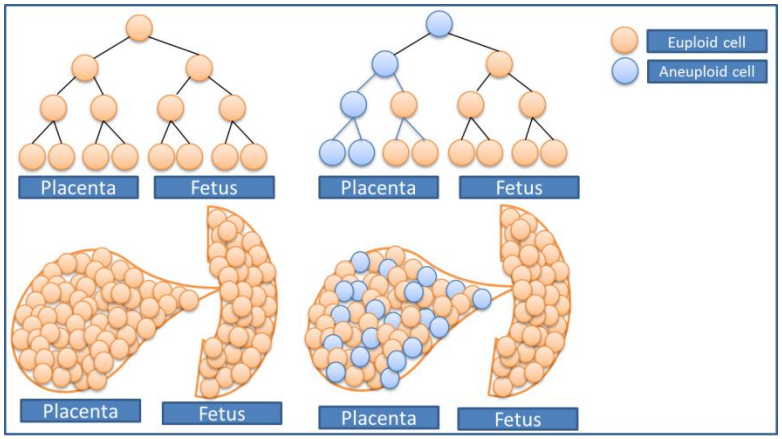


PGD Indications

- The procedure has also been offered to couples: undergoing IVF *at risk for aneuploidy*
  - maternal age > 35 years
  - Prior trisomic conception
- With *recurrent pregnancy losses*
- Prior *failed IVF cycles* (*>3 prior embryo transfers with high quality, morphologically normal embryos*)
- Requesting PGD for *HLA-typing* *(to allow selection of embryos that are histocompatible with live siblings)*
- Requesting *sex selection* for “family balancing”

Causes of Misdiagnosis

- **Human Error**
  - Unprotected sex
  - mislabeling, misidentification, misinterpretation
  - wrong embryo transfer
  - incorrect probes or primers
- **Technical**
  - Probe or primer failure
  - contamination (maternal, paternal, operator, carry-over)
- **Intrinsic (embryo)**
  - Mosaicism
  - Allele drop out
  - Uniparental Disomy

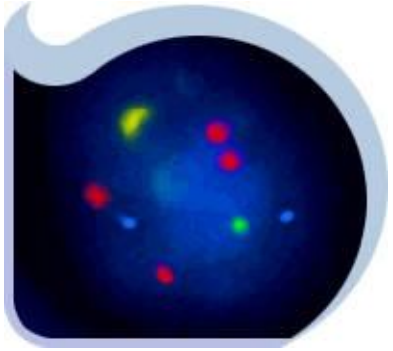


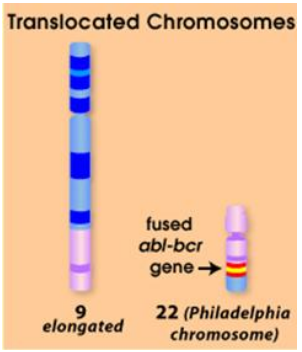
The Methods of Preimplantation Genetic Diagnosis

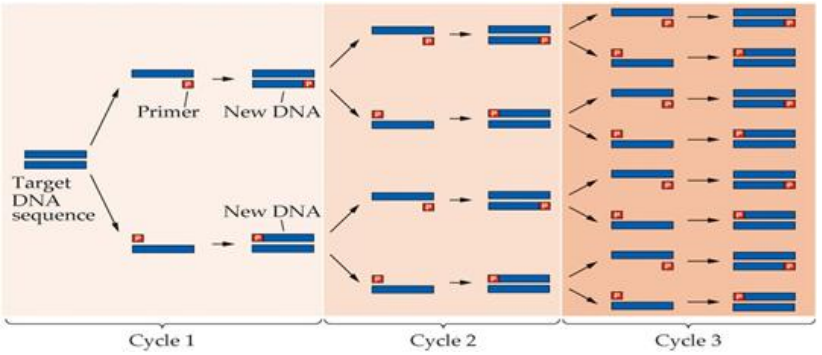
1. **Remove a single cell (blastomere.) from the 6-8-cell embryo**
2. **Two types of assessment techniques are common:**
   a. chromosome “painting” (or FISH)
   b. Genetic testing for specific disease loci (PCR or gene chips)

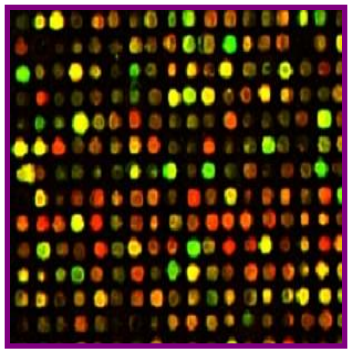
Limitations of PCR-based tests:

- Both alleles may not amplify equally, leading to misdiagnosis or inconclusive results
- PCR-based tests only detect disorders at target loci; other mutations may exist elsewhere
- Prenatal amniocentesis or CVSis usually recommended



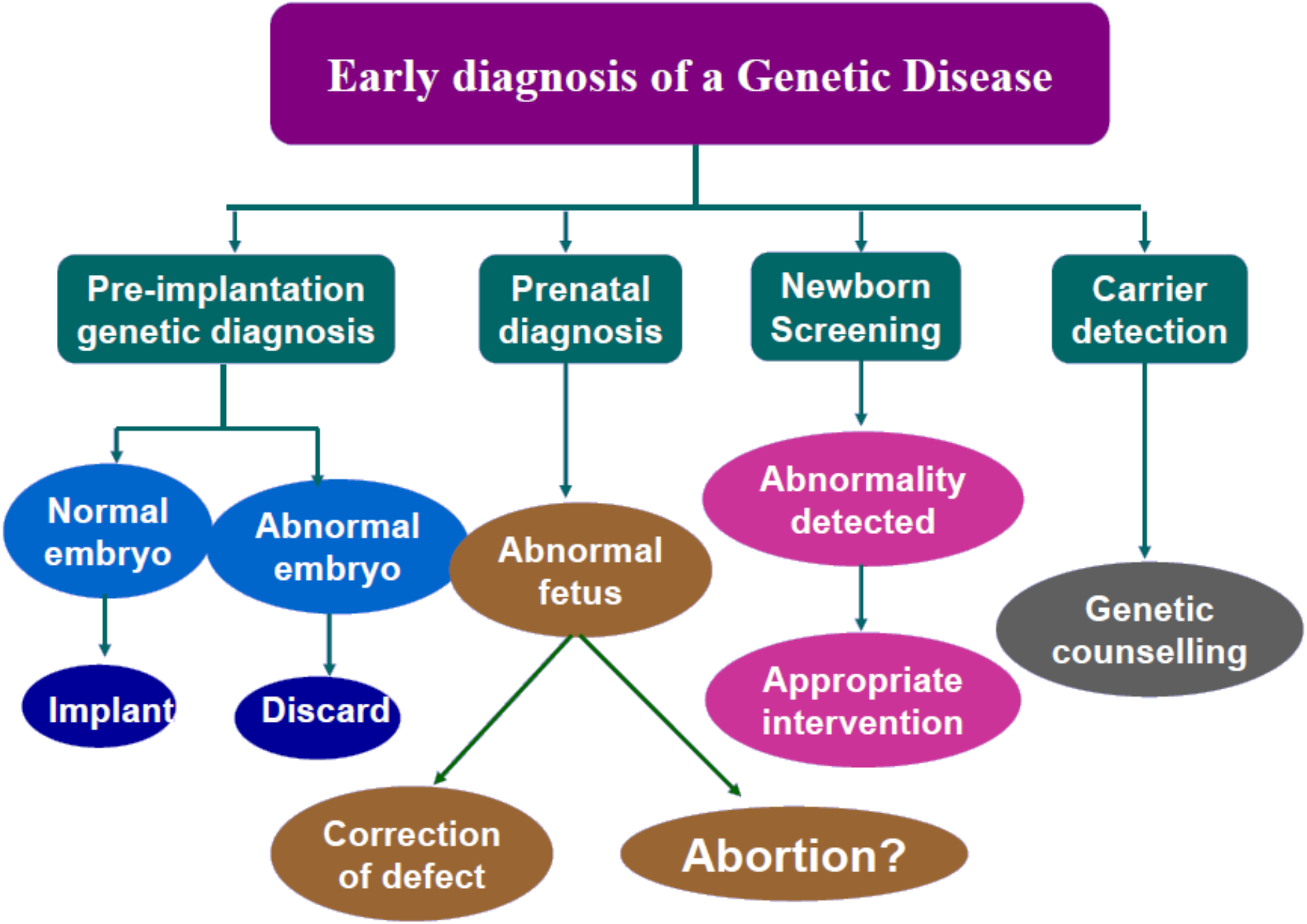






Risks to the child conceived via IVF/PGD:

- ✓ Low birth weight; premature birth
- ✓ Developmental delays
- ✓ Cognitive problems (ADHD)
- ✓ Urogenital problems
- ✓ Cerebral pals
- ✓ Certain cancers (e.g., Beckwith-Weidemann syndrome, which may be related to ICSI)


Early diagnosis of a Genetic Disease
Pre-implantation genetic diagnosis
Prenatal diagnosis
Newborn Screening
Carrier detection
Normal embryo
Abnormal embryo
Abnormal fetus
Abnormality detected
Genetic counselling
Implant
Discard
Appropriate intervention
Correction of defect
Abortion?

Models of Regulatory Frameworks for PGD

	Professional Guidelines	Facilitative Legislation	Restrictive Legislation	Prohibitive Legislation
Method of regulation	Voluntary Peer Review Process	Legislation and delegation to statutory body	Comprehensive legislation	Legislation banning procedures
Jurisdiction	USA New South Wales And Queensland Australia; India	UK Victoria Australia Canada New Zealand	France Slovenia Netherlands	Italy Germany Austria Switzerland Ireland

Extra Slide

- Because of the ethical and safety concerns raised by reprogenetic technologies, there has been added impetus for jurisdictions to determine their respective legal and policy positions in relation to reprogenetic technologies.

- Response to the regulation of PGD through out the world has been predictably varied. However, most jurisdictions have implemented some form of regulatory control.

- The spectrum of control runs from
  - a virtually free market system that is regulated only by professional self-regulation and the particular criminal or civil system (US),
  - to facilitative regimes with a broad legislative framework (NZ, UK)
  - to more precise frameworks derived from specific legislative initiatives, Restrictive frameworks are as precise as possible in terms of specifying acceptable use of pgd.
  - to complete prohibition.

- New Zealand has recently contributed to this regulatory and policy framework mix with the enactment of the Human Assisted Reproductive Technology Act 2004.

- Where PGD is banned, reproductive tourism occurs.

- **Counselling** A educational process by which patientsor/& at risk individuals are given information tounderstand the nature of the genetic disease, its transmission and the options open to them in management and family planning.
- Genetic counselling -an integral part of the management of patients and families with genetic disorders

Genetic Counselling

An essential component of health counselling

For control of diseases with partial or complete genetic aetiology

- Single gene disorders
- Chromosomal anomalies
- Multifactorial disorders
- Mitochondrial disorders

Essential Components of Genetic Counselling

History and pedigree construction

Clinical Examination

Confirmatory diagnosis

- History findings
- Clinical examination findings
- Radiology findings
- Laboratory parameter results
- DNA studies results
- Others

Calculation of recurrence risk

Counseling

Available options

Follow-up

The Genetic Counselling Process

Beneficiaries → **Individual or couple seeking counselling**

Why?
- Have affected child
- Are carriers
- Have genetic disease in family
- Have recurrent abortions
- High maternal/paternal age
- Exposed to a mutagen/teratoge
- Are consanguineous

Counselling elements

Reaching accurate diagnosis

- Family history
- Physical/clinical examination
- Cytogenetic studies/radiology
- Laboratory/DNA analysis

Estimation of recurrence risk

- Family pedigree
- Applying various risk calculation methods:
  - Bayesian
  - Mendels

Genetic counselling

- Available options
- Risk calculations
- New developments, etc.
- Disease course
- Treatment availability

Decision making

- Knowledge of disease recurrence
- Non-directive
- Available options
- Family pressure
- Religious beliefs
- Social status
- Economic status
- Community influence