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

Genetic Diseases (Control and Prevention)

Increase awareness

Genetic Screening

Appropriate management and consultation programmes

- High risk
- Premarital
- Prenatal
- Neonatal
- General populations

*Genetic Counselling*

- Patients, families and community
- Clinical staff and premedical personnel
- 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
- Article in Newspapers
- Radio, TV, Video documentation
- Inclusion Curriculae
- Doctor-patient meetings
- 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).
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

To prevent the birth of an affected child

Genetic Counselling

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

homozygous or double heterozygous
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

The ultimate goal is to reduce the birth incidence of beta-thalassemia in Jordan
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 thalassemia will be born annually.
Beta-thalassemia premarital screening program

Education of the public

Training of health personnel

Pre-screening Counseling

Screening test

Interpretation of test

Both or one non-carrier

Both are carriers

Report that test was done
Both are carriers

Confirmatory Test

Both are carriers

Both or one non-carrier

Counseling by Specialist

Non-stigmatization
Confidentiality
Autonomy of decision

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

- Screening for Hb S or β-thalassaemia

  - Both partners carriers

  - Genetic counseling

  - Prevent the birth of an affected child
Successful Programs

• Screening programs for $\beta$-thal.
  - In Greece and Italy have resulted in a drop in the incidence of affected homozygotes by almost 95%.
  - In Cyprus almost to 100%
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

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Test/method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylketonuria</td>
<td>Guthrie&quot; or automated fluorometric assay</td>
</tr>
<tr>
<td>Congenital hypothyroidism</td>
<td>Thyroxine or thyroid stimulating hormone</td>
</tr>
</tbody>
</table>

#### Other inborn errors
- Biotidinase deficiency         | Specific enzyme assay                            |
- **Galactosaemia**              | Modified Guthrie                                 |
- Homocystinuria                 | Modified Guthrie                                 |
- Maple syrup urine disease      | Modified Guthrie                                 |
- Tyrosinaemia                   | Modified Guthrie                                 |

#### Miscellaneous
- 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

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

Before 120th day

Acceptability of termination?
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
- Preimplantation 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 disease
- Cystic 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

• Detection rate in women
  ▪ <35: 60-75% for DS
  ▪ >35: 75% or more
  ▪ >80% for trisomy 18

• Positive screening rate 5%

“Triple”

“Quad”
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.

![Graph showing distribution of maternal serum AFP levels for Down syndrome and Spina bifida](image)
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 women
- 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

<table>
<thead>
<tr>
<th></th>
<th>T21</th>
<th>T18</th>
<th>T13</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Specificity (%)</strong></td>
<td>99-100</td>
<td>99-100</td>
<td>99-100</td>
</tr>
<tr>
<td><strong>Sensitivity (%)</strong></td>
<td>98-100</td>
<td>97-100</td>
<td>79-100</td>
</tr>
<tr>
<td><strong>Positive Predictive Value [PPV] (%)</strong></td>
<td>90-95*</td>
<td>84*</td>
<td>52*</td>
</tr>
<tr>
<td><strong>Negative Predictive Value [NPV] (%)</strong></td>
<td>99.9</td>
<td>99</td>
<td>100</td>
</tr>
</tbody>
</table>

*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
Increased Nuchal Translucency

Trisomies 21, 18, 13, triploidy and Turner syndrome

<table>
<thead>
<tr>
<th>NT measurement</th>
<th>Chance of normal birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 3.4mm</td>
<td>95%</td>
</tr>
<tr>
<td>3.5 – 4.4mm</td>
<td>70-86%</td>
</tr>
<tr>
<td>4.5 – 5.4mm</td>
<td>50-77%</td>
</tr>
<tr>
<td>5.5 – 6.4mm</td>
<td>67%</td>
</tr>
<tr>
<td>≥ 6.5mm</td>
<td>31%</td>
</tr>
</tbody>
</table>
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

Amniotic fluid withdrawn

- 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
Molecular Testing

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

<table>
<thead>
<tr>
<th>Technique</th>
<th>Timing</th>
<th>Miscarriage risk</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorionic villus sampling</td>
<td>11–14 weeks</td>
<td>~ 1 %</td>
<td>- chromosome analysis (karyotyping)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- molecular genetic diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- biochemical diagnosis</td>
</tr>
<tr>
<td>Amniocentesis</td>
<td>15–17 weeks</td>
<td>0.5 %–1 %</td>
<td>- chromosome analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- diagnosis of open neural tube defects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- molecular genetic diagnosis</td>
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<td></td>
<td></td>
<td></td>
<td>- biochemical diagnosis</td>
</tr>
<tr>
<td>Placentental biopsy</td>
<td>From 15 weeks</td>
<td>~ 1%</td>
<td>- chromosome analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- molecular genetic diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- biochemical diagnosis</td>
</tr>
<tr>
<td>Cordocentesis</td>
<td>from 16–20 weeks *¹</td>
<td>~ 1%</td>
<td>- chromosome analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- hematological and biochemical diagnosis</td>
</tr>
<tr>
<td>Fetal biopsy</td>
<td>from 20 weeks</td>
<td>*²</td>
<td>- diagnosis of specific genetic dermatoses</td>
</tr>
</tbody>
</table>
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
1. Ovary stimulated (multiple oocytes mature)

2. Egg and sperm retrieved

3. Fertilization

4. Embryo transferred into uterus

Cells divide in vitro

PGD at this stage
Preimplantation Genetic Diagnosis (PGD)

Eight-cell embryos

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

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 Hematopoietic Stem Cell Transplantation:
  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 CVS is 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
- Normal embryo: Implant
- Abnormal embryo: Discard

Prenatal diagnosis
- Abnormal fetus
  - Abnormality detected: Appropriate intervention
  - Abnormality detected: Genetic counselling

Newborn Screening
- Abnormality detected
  - Appropriate intervention

Carrier detection
- Genetic counselling

Abortion?
## Models of Regulatory Frameworks for PGD

<table>
<thead>
<tr>
<th>Method of regulation</th>
<th>Professional Guidelines</th>
<th>Facilitative Legislation</th>
<th>Restrictive Legislation</th>
<th>Prohibitive Legislation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jurisdiction</td>
<td>USA New South Wales And Queensland Australia; India</td>
<td>UK Victoria Australia Canada New Zealand</td>
<td>France Slovenia Netherlands</td>
<td>Italy Germany Austria Switzerland Ireland</td>
</tr>
</tbody>
</table>
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 throughout 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 patients or at risk individuals are given information to understand 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
  - History findings
  - Clinical examination findings
  - Radiology findings
  - Laboratory parameter results
  - DNA studies results
  - Others
- Confirmatory diagnosis
- Calculation of recurrence risk
- Counseling
- Available options
- Follow-up