Topic: MEDICAL AND GENETIC ASPECTS OF A FAMILY
Plan

1. Medical and genetic aspects of a family.
2. Medical and genetic counseling (MGC): the purpose and objectives.
3. Determining the degree of genetic risk. Assessment of the severity of medical and social consequences of heredity anomalies.
5. Newborn screening programs to detect hereditary metabolic disorders.
Recommended literature:


Hereditary disorders

1. **Chromosomal diseases** – those, that are caused by numerical or structural abnormalities of chromosomes (e.g. Down syndrome, Turner syndrome).

2. **Gene (molecular) diseases**, or **single gene disorders** – those, that are caused by defects of individual genes (e.g. thalassemia, haemophilia).

3. **Multifactorial diseases** (diseases with hereditary predisposition) – those, that are the result of the combined effect of genetic and envionmental factors (e.g. hypertension, diabetes mellitus).
Genetic diseases

traditionally - 3 types of diseases
1. genetically determined
2. environmentally determined
3. 1. + 2.

about 50% of spontaneous abortuses have chromosomal aberration

• hereditary = derived from parents
• familial = transmitted in the gametes through generations
• congenital = present at birth (not always genetically determined)
Chromosomal diseases

Chromosomal diseases = Chromosomal disorders occurs when there is a change in the number or structure of the chromosomes (numerical and structural disorders).

This change in the amount or arrangement of genetic information in the cells may result in disorder of growth, development or functioning of the body systems.

Usually is used term syndrome – a set of medical signs and symptoms which are correlated with each other and often associated with a particular disease or disorder.
Monogenic diseases

- Caused by the inheritance of a single defective gene
- Scientists currently estimate that over 10,000 of human diseases are known to be monogenic.
- Pure genetic diseases are caused by a single error in a single gene in the human DNA. The nature of disease depends on the functions performed by the modified gene.
Multifactorial diseases

- Interaction between **genetic** and environmental factors
- **Polygenic nature**: no single error in the genotype
- Environmental factors play a significant role in **precipitating** the disorder in genetically susceptible individuals.
- Tend to cluster in families.
- Do not follow to pedigree patterns of inheritance
- Cause the majority of morbidity and mortality in developed countries.
Genetic heterogeneity can be defined as mutations at two or more genetic loci that cause the same or similar phenotypes, which called **genocopies**. **Genocopy** refers to situation when identical phenotype is produced by two different genes / genotypes.

**Example:**
- Hearing loss may be due to one of 132 different genes that follow autosomal recessive inheritance

\[ \begin{align*}
BBrr & \quad \text{deaf} \\
bbRR & \quad \text{deaf} \\
BbRr & \quad \text{NOT deaf}
\end{align*} \]

B, b = gene for hearing loss type 1
R, r = gene for hearing loss type 2
Medical genetic counseling

Genetic counseling is the process of advising individuals and families affected by or at risk of genetic disorders to help them understand and adapt to the medical, psychological and familial implications of genetic contributions to disease.

The process integrates:

- Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence
- Education about inheritance, testing, management, prevention, resources
- Counseling to promote informed choices and adaptation to the risk or condition.
The term *genetic counseling* was coined in *1947* by Sheldon Clark Reed, who published the book «Counseling in Medical Genetics» in 1955.

Sheldon Clark Reed
(1910 – 2003)
Medical genetic counseling

**Genetic counseling is the process**

- evaluating family history and medical records
- ordering genetic tests
- evaluating the results of this investigation
- helping parents understand and reach decisions about what to do next
Medical genetic counseling

Genetic Counselling for Mendelian Disorders

- Genetic disorders:
  - Chromosomal
  - Single gene
  - Multifactorial
  - Mitochondrial
  - Acquired somatic

- Only single disorders follow a clearly defined pedigree pattern of inheritance “Mendelian Pattern”.

- During genetic counselling it is essential to establish whether or not the disorder is Mendelian and to calculate the precise risk of recurrence.
Prenatal diagnostics

Indications for prenatal genetic diagnosis

- 42.85% abnormal biochemical screening
- 4.76% fetal malformations observed at ultrasound evaluations
- 4.76% advanced maternal age
- 4.76% abnormal biochemical and ultrasound markers
- 38.09% advanced maternal age and family history of congenital malformations
- 4.76% advanced maternal age fetal malformations identified by ultrasound
Prenatal diagnosis is prescribed when:

- The pregnant woman is 35 years or older.
- She or her parents have had a previous child with a chromosomal abnormality.
- She has a history of recurrent abortions, or her husband's previous wife experienced several miscarriages.
- A history of parental consanguinity is present.
- The couple is known to be carriers of a chromosomal translocation.
- The pregnant woman is affected with type 1 diabetes mellitus, epilepsy, or myotonic dystrophy.
- She is exposed to viral infections, such as rubella or cytomegalovirus.
- The mother is exposed to excessive medication or to environmental hazards.
- In her or her spouse's family, a history of Down syndrome or some other chromosomal abnormality is present.
- A history of single gene disorder is present in her or her spouse's family.
- The fetus is detected to be at increased risk for a NTD (neural tube defects).
Benefits of Prenatal diagnostics:

- Prenatal diagnosis determines the outcome of pregnancy.
- It is helpful for couples to decide whether to continue the pregnancy.
- It indicates possible complications that can arise at birth process.
Prenatal diagnostics

Prenatal Diagnosis Techniques

Invasive
- Chorion Biopsy
- Amniocentesis
- Foetal blood sampling
- Biopsy of foetal tissue
- Embryofetoscopy

NON-invasive
- Ultrasound
- Doppler
- Maternal blood (biochemical markers)
- Maternal blood (foetus free-fetal DNA)
Noninvasive techniques

• Fetal visualization:
  • Ultrasound
  • Fetal echocardiography
  • MRI
  • Radiography

• Screening:
  • for neural tube defects (NTDs)
    • Measuring maternal serum alpha-fetoprotein (MSAFP)
  • for fetal Down syndrome
    • Measuring MSAFP
    • Measuring maternal unconjugated estriol
    • Measuring maternal serum beta-human chorionic gonadotropin (HCG)

• Separation of fetal cells from the mother's blood.
There are five types of prenatal genetic tests, which can be used for screening the risk of the baby having a genetic disorder or for diagnosing such abnormalities.

**FOR SCREENING**
- Evaluate the risk of genetic problems
- Non-invasive
- Offered to all women

1. Maternal blood serum
2. Prenatal ultrasounds
3. Non-invasive prenatal testing (NIPT)

**FOR DIAGNOSING**
- Confirm or rule out genetic problems
- Invasive
- Offered after abnormal screening tests or known risks factors

4. Chorionic villus sampling
5. Amniocentesis
Prenatal diagnostics

Prenatal Testing

Prenatal testing is an array of **routine and specialized tests** are aimed at monitoring fetal development, evaluating maternal health, assessing the risk of potential complications.

**1ST TRIMESTER TESTS**

- **First Prenatal Visit**
  - Pregnancy test
  - Blood test
  - Urine test
  - Dating ultrasound
- **1st Trimester Screening**
  - Maternal Blood Serum
  - Nuchal translucency

**2ND TRIMESTER TESTS**

- Urine test
- Fetal heart rate monitoring
- Glucose challenge screening
- Quad screen
- Anomaly ultrasound

**3RD TRIMESTER TESTS**

- Urine test
- Fetal heart rate monitoring
- Group B Strep Test
- Baby kick count

**NON-Routine**

- Cell-free DNA test
- Chorionic villus sampling

- Amniocentesis
- Glucose tolerance test

- Ultrasound
- Non-stress test
- Biophysical profile
- Contraction stress test

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Ultrasound (ultrasonography) is using high-frequency sound waves to produce an image of internal organs and tissues (sonogram).

1st Trimester Findings:
- normal evaluation of fetal number
- location of the placenta
- evaluation of the fallopian tubes and ovaries
- location of the pregnancy (intrauterine or ectopic)
- nuchal translucency
- measurement of the crown-rump length (CRL) or the gestational sac diameters

2nd and 3rd Trimester Findings:
- Head and intracranial anatomy
- Face
- Heart and chest
- Abdomen
- Kidneys
- Spine
- Extremities
- Placenta, amniotic fluid, uterus and other structures
Fetal echocardiography (echo, Doppler technique) uses sound waves to check the heart of developing baby.

- can be performed at 15 weeks' gestation and beyond;
- when this technique is used with duplex or color flow Doppler, it can identify a number of major structural cardiac defects and rhythm disturbances;
- recommended in:
  - Maternal diseases, such as diabetes or phenylketonuria associated with fetal structural heart defects, in particular heart blocks, such as lupus or other immune disorders;
  - Alcohol or drug consumption by mother during pregnancy;
  - Maternal rubella infection during pregnancy.
Magnetic resonance imaging (MRI) is a non-invasive imaging technology that produces three dimensional detailed anatomical images.

- this technique uses powerful magnets and radio waves to construct images of the body, but, because of fetal movements, its application has been limited.
Radiography is an imaging technique using X-rays, gamma rays, or similar ionizing radiation and non-ionizing radiation to view the internal form of an object.

- The fetal skeleton can be visualized by radiography from 10 weeks' gestation onward. This technique is used for the diagnosis of inherited skeletal dysplasias, particularly osteochondrodysplasia, in the 2nd and 3rd trimesters.
- Because of the dangers of radiography to the fetus, this technique rarely is used.
Prenatal Testing

Non-invasive and invasive tests used during pregnancy for the identification of OI and other birth anomalies.

**Chorionic villus sampling (CVS)**
An invasive sampling of the placental tissue for further genetic analysis of OI.
Used from 10th-12th weeks of gestation.

**Non-invasive prenatal testing (NIPT)**
NIPT uses fetal DNA from the mother's bloodstream for prenatal testing of OI.
Used from 7th-10th weeks of gestation.

**Cordocentesis**
An invasive sampling of umbilical cord blood for further OI genetic analysis.
Used on 22nd-24th weeks of gestation.

**Ultrasound**
Allows to discover severe OI cases from 20th weeks of gestation non-invasively.

**Amniocentesis**
An invasive sampling of amniotic fluid for further OI genetic analysis.
Used from 15th-20th weeks of gestation.
**Noninvasive Prenatal Testing (NIPT)**

NIPT is a prenatal screening test that can be performed beginning around the 10th week of pregnancy.

- **Fetus**
- **Placenta**
- **Small fragments of cell-free DNA from the placenta enter the mother’s bloodstream.**

- **Placental (“fetal”) DNA**
- **Maternal DNA**

Cell-free DNA in a sample of the mother’s blood is analyzed for evidence of extra or missing fetal DNA segments.

- **Woman**
- **Maternal DNA**
- **Noninvasive prenatal testing**
- **Fetus**
- **Cell-free DNA in blood**
Maternal screening

Tripple screening
- HCG
- AFP
- Estriol

Quadruple screening
- HCG
- AFP
- Estriol
- Inhibin A

Screening methods

Source
-AFP -> Fetus
-HCG -> Placenta
-Estriol -> Fetus + Placenta
Alpha-fetoprotein (AFP) test

Blood is withdrawn from vein between the 16-18 weeks of pregnancy

AFP:  
-  
+  

- To detect liver cancer
- Other chromosomal abnormalities
- Defects in the abdominal wall of the fetus
- To screen for neural tube defect (high level AFP)
- To screen for Down’s syndrome (low level AFP)

α-FP

- Increased with:  
  Neural Tube Defects (NTD) fetal malformation and also twin gestation;

- Decreased with:  
  Trisomy 21 and Trisomy 18
Human chorionic gonadotropin (HCG)

- Glycoprotein
- Molecular weight is 36000-40000 daltons.
- produced by the placental trophoblastic cells made of two subunits – alpha and beta.
- $\alpha$-HCG, produced by cytotrophoblasts, structurally resembles follicle-stimulating hormone, leutinizing hormone, and thyroid-stimulating hormone.
- $\beta$-HCG, made by syncitiotrophoblasts, is the clinical marker of pregnancy.

Increased in Trisomy 21
Decreased in Trisomy 18
Unconjugated Estriol (UE3)

- Hormone produced in large amounts by the placenta during pregnancy.
- It tests the function of the placental unit.
- It is also made by the baby’s adrenal glands.
- Peaks at 40 weeks gestation
- Diabetics tested at 32 weeks to determine placental function.
- Decreased in Trisomy 21 and Trisomy 18
Hormone inhibin A

- Added in the quadruple screening test
- Protein produced by the fetus and placenta
- **Abnormally high inhibin A can be a sign of Down syndrome**
- Detects almost 86% of all Down syndrome cases (more sensitive)
Screening for fetal Down syndrome

Triple screening:
– Measuring MSAFP
– Measuring maternal unconjugated estriol
– Measuring maternal serum beta-HCG

Others screening techniques:
• Pregnancy associated plasma protein - A (PAPP-A)
• Inhibin A
Of note! We need to look at the whole picture, since some of the tests may be normal and others abnormal

- Decreased AFP = Trisomy 21 or 18 (increased with Neural Tube Defects (NTD)- fetal malformation – also twin gestation)
- Decreased Estriol = Trisomy 21 or 18
- Increased HCG = Trisomy 21 (decreased with Trisomy 18)
- Increased inhibin A = Trisomy 21
Invasive techniques

• Fetal visualisation
  • Embryoscopy
  • Fetoscopy
• Fetal tissue sampling
  • Amniocentesis
  • Chorionic villus sampling (CVS)
  • Percutaneous umbilical blood sampling (PUBS)
  • Percutaneous skin biopsy
  • Other organ biopsies, including muscle and liver biopsy
• Preimplantation biopsy of blastocysts obtained by *in vitro* fertilization
Invasive prenatal diagnostics

- Chorionic villi sampling (CVS)
- Amniocentesis
- Cordocentesis

Prenatal examinations:

- Chorion
- Umbilical cord
- Amnion

Weeks of pregnancy:

- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24
Embryoscopy

• In this technique, a rigid endoscope is inserted via the cervix in the space between the amnion and the chorion, under sterile conditions and ultrasound guidance, to visualize the embryo for the diagnosis of structural malformations.

• It is performed in the first trimester of pregnancy (up to 12 weeks’ gestation).
Fetoscopy

• In this technique, a fine-caliber endoscope is inserted into the amniotic cavity through a small maternal abdominal incision, under sterile conditions and ultrasound guidance, for the visualization of the embryo to detect the presence of subtle structural abnormalities. It also is used for fetal blood and tissue sampling.

• It is performed during the second trimester (after 16 weeks’ gestation).

• Fetoscopy is associated with a 3-5% risk of miscarriage; therefore, it is superseded by detailed ultrasound scanning.
Amniocentesis

Sampling of small amount of amniotic fluid through transabdominal needle aspiration; after 16 weeks.

Used to diagnose NTDs and genetic disorders, including down’s syndrome.

Risk: fetal loss (1/200 to 1/300); chorioamnionitis; fetal injury; alloimmunization; ROM.

Replaced with quad screen (measure maternal proteins) and cell-free DNA (detect fetal DNA in mom’s circulation).
Amniocentesis

What Is Amniocentesis?

It is a procedure in which amniotic fluid is removed from the mother’s uterus for testing and treatment.

1. Amniotic fluid surrounds and protects the fetus in the womb.
2. This fluid contains fetal cells and various chemicals produced by the fetus.
3. The fetal samples are tested for possible abnormalities in the fetus.

Why is it being performed?

Amniocentesis tests for the following:
- Chromosomal abnormalities
- Inherited genetic diseases
- Lung maturation
- Evaluate for infection or illness
- Decrease volume of amniotic fluid

Most common: Chromosomal abnormalities, Inherited genetic diseases

Very rarely: Lung maturation, Evaluate for infection or illness, Decrease volume of amniotic fluid
Chorionic villus sampling (CVS)
Chorionic Villus Sampling

Chorionic villus sampling is a **prenatal genetic testing** that can be offered to women between the 10th and 13th weeks of pregnancy to confirm or rule out that their child has certain genetic conditions.

**WHAT IT TESTS FOR**

- **Chromosomal abnormalities:**
  - Down syndrome
  - Edward’s syndrome

- **Genetic conditions:**
  - Cystic fibrosis
  - Sickle cell anemia

**PROCEDURE**

Consists of withdrawing a small **sample of placental tissue** in one of two ways:

- Transcervical
- Transabdominal

**RISKS**

- **Miscarriage:** 1 in 100 pregnancies
- Rare or mild side effects:
  - Dizziness
  - Infection
  - Abdominal cramps
  - Rh incompatibility

**RESULTS**

- Preliminary results are ready in **2-3 days**;
  - Complete analysis in about 10 days
- **CVS** is **98-99%** accurate

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Cordocentesis
(Percutaneous umbilical (fetal) blood sampling(PUBS))

- Removal of blood from umbilical cord
- Rarely done
- Done when diagnostic information can not be obtained through amniocentesis, CVS, US or the results of these tests were inconclusive
- Performed after 17 weeks
- Potential indications: suspected fetal infection, anemia, thrombocytopenia
- Loss rate - 2%
Summary of invasive methods

**Amniocentesis**
Chromosome/micro-array and DNA analysis
Fetal infection – PCR

**Fetal blood sampling**
Fetal haemoglobin for anaemia
Fetal infection serology
Fetal blood transfusion

**Chorionic villus sampling**
Chromosome/micro-array and DNA analysis
Fetal infection – PCR
Enzyme analysis of inborn error of metabolism

**Preimplantation genetic diagnosis (PGD)**
In vitro fertilisation allows genetic analysis of cells from developing embryo before transfer to the uterus

**Fetoscopy**
Minimally invasive surgery, e.g. laser photo-coagulation of communicating vessels in twin–twin transfusion syndrome.

**Non-invasive genetic diagnosis – free fetal DNA from maternal blood**
Identification of fetal gender and rhesus status
Invasive prenatal diagnostics

Schedule of prenatal examinations

- 12th – 20th week
  - Ultrasound

- 16th week
  - Biochemical test
    - AFP, hCG, E3, PAPP

- 20th week
  - Cordocentesis

- 20th week
  - Amniocentesis

- 11th week
  - Chorionic villi sampling

End of prenatal examinations

Pregnancy (weeks)
# Incidence of Sex Chromosome Abnormalities

<table>
<thead>
<tr>
<th>Sex</th>
<th>Disorder</th>
<th>Karyotype</th>
<th>Approximate Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Klinefelter syndrome</td>
<td>47,XXY</td>
<td>1/1000 males</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48, XXXY</td>
<td>1/25,000 males</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others (48, XYY; 49, XXXYY; mosaics)</td>
<td>1/10,000 males</td>
</tr>
<tr>
<td></td>
<td>47,XYY syndrome</td>
<td>47,XYY</td>
<td>1/1000 males</td>
</tr>
<tr>
<td></td>
<td>Other X or Y chromosome abnormalities</td>
<td></td>
<td>1/1500 males</td>
</tr>
<tr>
<td></td>
<td>XX males</td>
<td>46,XX</td>
<td>1/20,000 males</td>
</tr>
<tr>
<td></td>
<td><strong>Overall incidence: 1/400 males</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Turner syndrome</td>
<td>45,X</td>
<td>1/5000 females</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46,X,i(Xq)</td>
<td>1/50,000 females</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others (deletions, mosaics)</td>
<td>1/15,000 females</td>
</tr>
<tr>
<td></td>
<td>Trisomy X</td>
<td>47,XXX</td>
<td>1/1000 females</td>
</tr>
<tr>
<td></td>
<td>Other X chromosome abnormalities</td>
<td></td>
<td>1/3000 females</td>
</tr>
<tr>
<td></td>
<td>XY females</td>
<td>46,XY</td>
<td>1/20,000 females</td>
</tr>
<tr>
<td></td>
<td>Androgen insensitivity syndrome</td>
<td>46,XY</td>
<td>1/20,000 females</td>
</tr>
</tbody>
</table>
Gene therapy

As we know:

- The basic unit of heredity
- Are carried on a chromosome
- Encode how to make protein
- Proteins carry out most of the functions of life.
- When there is a mutation in the gene, changes in the conformation and functions of the protein lead to diseases.
Gene therapy is the introduction, using a vector, of nucleic acids into cells with the intention of altering gene expression to prevent, halt or reverse a pathological process.
Gene therapy

Types Of Gene Therapy

- Somatic gene therapy
  transfer of gene into somatic cell such as organs

- Germline gene therapy
  gene transfer into germ cells (sperm and ova)
Gene therapy methods

**in vivo**
- Therapeutic gene
- Less invasive procedure
- Directly tackle proliferative tumor cells to inhibit cell division
- Depending on the vector
- Selection of target cells
- Immunocompatibility (autologous cells)
- Requires an invasive procedure for solid tumors
- Non-proliferative altered tumor cells will not outgrow over highly proliferative tumor cells
- Require the targeting of tumor cells
- Possible immune responses to gene vectors

**ex vivo**
- Cells removed from patient and cultured
- Cells transfected with therapeutic gene
- Modified cells introduced in the patient
- ✗ Require the targeting of tumor cells
- ✗ Possible immune responses to gene vectors
Gene therapy methods

Ex vivo gene therapy is performed with the genetic alterations of patient's target cells happening outside of the body in a culture. Target cells from the patient are infected with a recombinant virus containing the desired therapeutic gene. These modified cells are then reintroduced into the patient's body, where they produce the needed proteins that correspond to the inserted gene.

Inside the body, the genetically altered cells produce the desired proteins encoded by the therapeutic DNA.
In Vivo Gene Therapy

In vivo gene therapy involves introduction of therapeutic DNA directly into the patient's body. The DNA is introduced by cell-specific direct injection into tissue in need. DNA in the form of a plasmid vector is introduced by a dermal vaccination. Modified liposomes are not currently used for gene therapy, but they will likely be the next advancement in therapeutic gene delivery as cell-specific receptor-mediated DNA carriers. Once inside the body and in contact with the specifically targeted cells, the inserted DNA is incorporated into the tissue's cells where it encodes the production of the needed protein.

1. Copies of therapeutic gene are inserted into viral DNA, liposome, or in form of plasmid DNA.

2. Genetically altered DNA is inserted into patient's body by cell-specific direct tissue injection.

3. Inside the body, the inserted DNA is incorporated into the cells of the specific tissue it was injected into. These cells now encode and produce the needed protein encoded by the inserted gene.
Vectors for gene therapy

- In general, a genetic material (DNA or RNA) is inserted into a person’s cell using a carrier, or vector. Vector systems can be divided into:

  - Viral Vectors
  - Non-viral Vectors

**SOME OF THE VIRAL VECTORS FOR GENE THERAPY**

- Adenoviral vectors.
- Adeno-associated viral vectors.
- Retroviral vectors.
- Alpha viral vectors.
- Herpes virus vectors.
- Vaccinia Viral Vectors.
Basic principle of gene therapy
### Diseases treated by gene therapy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Defect</th>
<th>Target cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe combined immunodeficiency</td>
<td></td>
<td>Bone marrow cells or T-lymphocytes</td>
</tr>
<tr>
<td>Hemophilia</td>
<td></td>
<td>Liver, muscle</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td></td>
<td>Lung Cells</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td>Many cell types</td>
</tr>
<tr>
<td>Neurological diseases</td>
<td>Parkinson’s/Alzheimer’s</td>
<td>Nerve Cells</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>AIDS, hepatitis B</td>
<td>White Blood Cells</td>
</tr>
</tbody>
</table>
Problems with gene therapy

Short Lived
Would have to have multiple rounds of therapy

Immune Response
New things introduced leads to immune response
Increased response when a repeat offender enters

Viral Vectors
Patient could have toxic, immune, inflammatory response
Also may cause disease once inside

Multigene Disorders
Heart disease, high blood pressure, Alzheimer’s, arthritis and diabetes are hard to treat because it needs to introduce more than one gene.

Induce tumor if integrated in a tumor suppressor gene because of insertional mutagenesis.
Prospects of gene therapy

- Overall impact on patient’s life
- Avoidance of readministration
- Reduction of effect immunogenicity
- Long-term safety, including tumour risk
- Plans to demonstrate comparability
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