1. Molecular basis of human genetics
   a) Structure and function of the human genome
      i. Fundamental insights derived from prokaryotic and eukaryotic genomes. Various levels of analysis: epigenome, genome, chromatin, chromosome, transcriptome, proteome, metabolome.
      ii. The genome of eukaryotes: exon-intron structure, repetitive DNA, etc. Structure of the human genome, regulation of gene activity, principles of gene mapping, significance of the human gene map.
      iii. Pathological and neutral genetic variation at the DNA level: polymorphisms, mutations.
   b) Transcription and translation
      i. DNA and RNA: flow of genetic information from DNA to RNA.
      ii. RNA-processing: splicing, alternative splicing, RNA-editing.
      iii. Protein synthesis: transport of mRNA from nucleus to cytoplasm, ribosomes, tRNAs, synthesis of polypeptide chains.
      iv. Biologically active proteins: correlation between structure, function and modification of biologically active polypeptides and proteins.
      vi. Gene expression analysis.
      vii. Microarray technology.
   c) Mutations and their consequences for human health
      i. Classification of mutations: Genome mutations, chromosome mutations, gene mutations.
      ii. Types of gene mutations: point mutations, splicing mutations, deletions, insertions, dynamic mutations (triplet expansions), frame shift mutations, missense and nonsense mutations, imprinting.
      iii. Causes of mutations.
      vi. Induced mutations: role of ionizing radiation, chemicals and viruses.
      vii. Genotype-phenotype correlations.
      viii. Functional consequences of gene mutations: consequences of type and localization of amino-acid substitutions on protein structure and function; haploinsufficiency, dominant-negative effects.
      ix. Multiple alleles: different mutations involving identical genes.
      x. Temporal and local differences of gene action during embryogenesis (e.g. different types of hemoglobins during ontogenesis). Differences of gene expression as basis of cellular and organ differentiation (e.g. Limitation of phenylalanine hydroxylase expression to liver cells).
   d) DNA analysis – diagnostic applications
      i. Principles of DNA-analysis: DNA and RNA isolation, restriction endonucleases, DNA sequencing, hybridization, direct and indirect gene analysis analysis via DNA sequencing and flanking markers, detection of mutations via application of the polymerase chain reaction (PCR) and of restriction fragment length polymorphisms (RLFP), including application of pre-screening techniques.
      iv. Indirect mutation analysis.
2. Cytogenetics

a) The human chromosome complement

i. Analysis and characterization of human chromosomes: tissues suitable for chromosome analysis, specialized chromosome structures: centromeres, telomeres, euchromatin, heterochromatin, epigenetic factors and chromatin organization, mechanisms leading to microdeletions, organization of human acrocentric chromosome short arms, gene arrangements on human chromosomes, artificial human chromosomes

ii. Chromosome structure as it relates to chromosome function

iii. Chromosome preparation and chromosome identification: cell culture and cell harvests, banding techniques, the human karyotype, transposons and transposable elements; fluorescence in situ hybridization (FISH), spectral karyotyping (SKY); light microscopy, digital image analysis, flowcytometry, comparative genome hybridization (CGH), identification of microdeletions.

iv. Nomenclature of chromosome aberrations

v. Structural variants of human chromosomes: clinical significance

vi. Organization of chromosomes and chromatin within the cell nucleus: nuclear matrix proteins, chromosomal topography of interphase nuclei

vii. Chromosomes and cell cycle: synchronous vs. asynchronous replication; mitosis, meiosis, molecular mechanisms of cell division: genes and proteins participating in mitotic chromosome segregation.

viii. Gonosomes: evolution of sex chromosomes, X and Y chromosomes

ix. Chromosome evolution: chromosome counts in different species, comparative cytogenetics, comparative chromosome mapping, animal models.

x. Limitations of cytogenetic analysis

xi. Chromosome aberrations

xii. Nondisjunction: factors influencing the distribution of chromosomes; mechanisms and consequences of meiotic nondisjunction (e.g. maternal age); mechanisms and consequences of mitotic nondisjunction (mosaicism, chromosomally aberrant cell clones giving rise to cell selection); uniparental disomy (UPD)

xiii. Numerical aberrations of human gonosomes: clinical pictures and karyotypes 45, X (monosomy X, Ullrich-Turner syndrome); 47, XXX (triple X syndrome), 47, XXY (Klinefelter syndrome), 47, XYY karyotype; significance of gonosomal mosaics; lack of correlation with maternal age due to preferential postmeiotic origin of the monosomy X Ullrich-Turner syndrome; cytogenetic variants of the Ullrich-Turner syndrome (Iso Xq chromosome, Xp and Xq deletions, ringX); high rate of spontaneous abortion in monosomy X pregnancies.

xiv. Numerical aberrations of human autosomes and their clinical consequences: Robertsonian translocations, reciprocal translocations, other structural aberrations; chromosome deletions: partial monosomy 5p (Cri-du-Chat syndrome), partial monosomy 4p (Wolf-Hirschhorn syndrome); autosomal microdeletion syndromes

xv. Chromosome aberrations as frequent cause of spontaneous abortion: most frequent common symptoms of autosomal chromosomal imbalance: developmental abnormalities, growth retardation; dysmorphic signs, congenital malformations; aberrant dermatoglyphics

xvi. Somatic chromosome aberrations: chromosome breakage following exposure to elastogens (chemicals, viruses, ionizing radiation). Human chromosome breakage syndromes (Fanconi anemia, Bloom syndrome, Ataxia telangiectasia, Nijmegen breakage syndrome)

3. Formal genetics and statistical genetics
a) Mendelian inheritance
i. autosomal dominant inheritance: definition and transmission of dominant traits; frequency, new mutations, clinical examples of dominant genes: irregular dominant inheritance; genetic basis of morphological disturbances; “sporadic cases” as new mutations (e.g. achondroplasia, neurofibromatosis, tuberous sclerosis); special features of autosomal dominant inheritance: penetrance, expressivity, late manifestations, pleiotropy, anticipation. Risk for offspring of gene carriers depending on complete or reduced penetrance; risk for offspring of healthy siblings of gene carriers; risk for offspring of healthy siblings of affected individuals; risk for additional offspring of healthy parents having a previous child expressing an autosomal dominant trait. Possibilities and limitations of molecular testing.

ii. Autosomal recessive inheritance: Definition and mode of transmission of recessive traits; recurrence risks, incidence; clinical examples of autosomal recessive disease; clinical significance of recessive alleles; consanguinity, pseudodominance, heterozygote testing, effects of homozygosity and heterozygosity; DNA-based diagnosis; genetic heterogeneity; characteristics of disorders with autosomal-recessive inheritance; clinically important examples; typical presentation of autosomal recessive disorders as single cases in small families; role of consanguineous marriages for the occurrence of recessive conditions; incidence of recessive disorders within certain ethnic groups (e.g. Tay-Sachs gangliosidosis); compound heterozygosity and risk for relatives; molecular genetic diagnosis of recessive disorders

iii. X-linked inheritance: Definition and mode of transmission of X-chromosomal traits; incidence, clinical examples; explanation for relative rarity of female carriers of X-chromosomal traits: high rates of new mutations; clinical relevance of carrier diagnosis; outline and examples of X-chromosomal dominant inheritance

iv. X-inactivation: Lyon-hypothesis; implications of lyonization; mode and extent of inactivation of X-chromosomal genes; genes that escape inactivation: pseudo-autosomal regions, X-Y homologous genes; implications for carrier females

b) mitochondrial inheritance
i. important disease examples of mitochondrial inheritance; heteroplasmy, mitochondrial bottlenecks; pedigrees suggestive of mitochondrial inheritance (e.g. Leber atrophy)

c) multifactorial inheritance
i. pattern of inheritance of common traits: body height, intelligence, genetic models, body height as example of multifactorial inheritance; correlation among relatives; significance of the environment: nature vs. nurture

ii. natural history of multifactorial diseases: genetic predisposition, incidence, variable manifestation, dependence on the environment, possibility of therapeutic modulation, recurrence risks among relatives, important examples: adiposity, diabetes mellitus, high blood pressure, non-syndromal mental retardation

iii. threshold effect and multifactorial inheritance

iv. comparison between multifactorial and monogenic inheritance: important examples, relative preponderance compared to monogenic disorders, gender differences in the manifestation of multifactorial disease (e.g. hip-joint dislocation, pyloric stenosis)
v. recurrence risks: definition of empirical risks, risk estimates as function of degree of relatedness, important examples

d) **Twins in human genetic research**


e) **Population genetics and genetic epidemiology**

i. population: definition in terms of genetics

ii. gene frequency: principle of gene and heterozygote frequency estimates in recessive conditions applying the Hardy-Weinberg rule; requirements for the assumption of Hardy-Weinberg equilibrium and important reasons for deviations from theoretical expectations

iii. Gene frequency differences among different populations: selection, isolation, genetic drift, migration, founder effects, assortative mating

iv. Hardy-Weinberg rule

v. Interaction between mutation and selection: implications for the distribution of genes and diseases in populations; mutation-selection equilibrium; heterozygote advantage; role of exogeneous factors (including medical factors) on disease prevalence

vi. Genetic association and linkage groups: definition, genetic basis, mutations with variable phenotypic effects, relative risk, attributable risk

vii. linkage analysis and gene mapping

viii. Human genome project

4. Genetic diagnosis and genetic counselling

a) **Specific aims of clinical genetics:** possibilities and limitations of genetic counselling

b) **Genetic counselling:** symbols used in pedigree drawing; estimation of recurrence risks, familiarity with psychological and other aspects of genetic counselling (e.g. severity and impact of genetic diseases; therapeutic possibilities, including side-effects; significance of pathological investigations of pregnancy losses

i. predictive genetic counselling: specific aspects of late-onset diseases and familial cancer syndromes

ii. Data banks: significance of data banks and confidentiality rules

c) **Prenatal diagnosis**

i. Methods: principles of prenatal diagnosis; non-invasive methods: sonography, maternal blood testing, triple- and integrated test; invasive methods: chorionic villus biopsy (CVS), amniocentesis, placentacentesis, umbilical cord blood, chromosome analysis, biochemical analysis of amniotic fluid, molecular genetic analysis, choice and risk of a given approach to prenatal diagnosis

ii. Indications for prenatal diagnosis: advanced maternal age, chromosomal aberrations in parents or offspring, increased risk for recognizable birth defects (e.g. malformation of the central nervous system, anencephaly, myelomeningocele), inborn errors of metabolism in the family, genetic diseases amenable to DNA-diagnosis

iii. Practical issues: genetic counselling, risk stratification, follow-up investigations

d) **Syndromology:** definitions, basics of intrauterine development, malformation vs. deformation, malformation sequence, dysmorphic signs; London dysmorphology- and other databases, search strategies
e) Developmental genetics: insights from human and animal development

5. Special topics in clinical genetics
a) gender differentiation and sexual development: gonosomal and autosomal genes; significance of chromosomal aberrations in sexual development; single gene defects causing disturbance of gonadal development (e.g. SRY-gene mutations; XX-males, XY-females, sex-reversal); androgen insensitivity syndromes due to androgen receptor gene mutations: complete, partial and mild ("testicular feminization"); consequences of prenatal androgen excess due to 17- and/or 21- hydroxylase deficiency: adrenogenital syndrome (AGS). Criteria for gender assignments (genetic, somatic, social, legal)

b) Genetics of Cancer
i. genetic aspects of tumorigenesis: oncogenes, tumor suppressor genes, loss of heterozygosity (LOH), loss of imprinting (LOI), Knudson two-hit hypothesis, Vogelstein model of colorectal tumorigenesis, gatekeepers and caretakers, chromosomal instability neoplasia (CIN), microsatellite instability neoplasia (MIN)
ii. Tumorcytogenetics: clonal origin of neoplastic cell growth, specific chromosome translocations in haematological neoplasia, aneuploidy and polyploidy as hallmark of solid tumors; chromosome- and gene amplifications (e.g. “double minute” chromosomes). Genetic mechanisms of resistance to chemotherapy, multidrug resistance.
iii. Monogenetic neoplastic disease: involvement in carcinomas of the breast, ovary, pancreas, prostate, colon, thyroid and other endocrine neoplasia (MEN)

c) Teratogenic and mutagenic effects on development: potential and effective teratogenic risks for embryo and foetus due to intrauterine exposure, chemical agents, defective metabolism, viral infections, and ionizing radiation. Approaches to the recognition of putative teratogenic effects; spectrum of proven teratogenic agents. Fetal alcohol syndrome.

d) Pharmacogenetics: variability of drug action due to genetic polymorphisms in drug detoxifying genes (e.g. p450); slow and fast metabolizers. Enzyme defects as cause of differential degradation of pharmacological agents. Clinically important examples. Limitations of genetic testing and interpretation of test results in pharmacogenetics.

e) Genetics of complex diseases

f) Genetics of ageing: loss of genetic homeostasis due to thermoinstability of DNA and formation of reactive oxygen species; accumulation of DNA lesions; lack of selection against late-onset genetic diseases; antagonistic pleiotropic gene action

g) Determination of genetic identity and descent: use of genetic polymorphisms; DNA fingerprinting

h) Basic preventive measures in human genetics: newborn screening for inborn errors of metabolism, treatment in retinoblastoma, avoidance of common diseases due to overnutrition or lack of exercise; preventive measures: change of nutrition and lifestyle; supportive measures during early childhood

i) Therapy of inherited disease: gene therapy, natural gene therapy (somatic reversion) protein replacement therapy, antisense strategies, hematopoietic stem cell transplantation (HSCT), surgical measures, tailored pharmacological agents (e.g. cystic fibrosis; stop-codon readthrough strategies); psychological issues, family support groups.