UNION EUROPÉENNE DES MÉDECINS SPÉCIALISTES
EUROPEAN UNION OF MEDICAL SPECIALISTS

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European Training Requirements for the Specialty of Medical Genetics

European Standards of Postgraduate Medical Specialist Training
Revised Version 2023

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Preamble

The Union Européenne des Médecins Spécialistes / Union of European Medical Specialists (UEMS) is a non-governmental organization representing national associations of medical specialists at the European level. With a current membership of 41 national associations and operating through 43 Specialist Sections and European Boards, the UEMS is committed to promoting the free movement of medical specialists across Europe while ensuring the highest level of training which will pave the way to the improvement of quality of care for the benefit of all European citizens.

The UEMS areas of expertise notably encompass Continuing Medical Education, Post Graduate Training and Quality Assurance. It is the UEMS' conviction that the quality of medical care and expertise is directly linked to the quality of training provided to the medical professionals. Therefore the UEMS committed itself to contribute to the improvement of medical training at the European level through the development of European Standards in the different medical disciplines. No matter where doctors are trained, they should have at least the same core competencies.

In 1994, the UEMS adopted its Charter on Post Graduate Training aiming at providing the recommendations at the European level for good medical training. Made up of six chapters, this Charter set the basis for the European approach in the field of Post Graduate Training. With five chapters being common to all specialties, this Charter provided a sixth chapter, known as “Chapter 6”, that each Specialist Section was to complete according to the specific needs of their discipline. More than a decade after the introduction of this Charter, the UEMS Specialist Sections and European Boards have continued working on developing these European Standards in Medical training that reflects modern medical practice and current scientific findings. In doing so, the UEMS Specialist Sections and European Boards did not aim to supersede the National Authorities' competence in defining the content of postgraduate training in their own State but rather to complement these and ensure that high quality training is provided across Europe.

At the European level, the legal mechanism ensuring the free movement of doctors through the recognition of their qualifications was established back in the 1970s by the European Union. Sectorial Directives were adopted and one Directive addressed specifically the issue of medical training at the European level. However, in 2005, the European Commission proposed to the European Parliament and Council to have a unique legal framework for the recognition of the Professional Qualifications to facilitate and improve the mobility of all workers throughout Europe. This Directive 2005/36/EC established the mechanism of automatic mutual recognition of qualifications for medical doctors according to training requirements within all Member States; this is based on the length of training in the Specialty and the title of qualification. Given the long-standing experience of UEMS Specialist Sections and European Boards on the one hand, and the European legal framework enabling Medical Specialists and Trainees to move from one country to another on the other, the UEMS is in a unique position to provide specialty-based recommendations. The UEMS values professional competence as “the habitual and judicious use of communication, knowledge, technical skills, clinical reasoning, emotions, values, and reflection in daily practice for the benefit of the individual and community being served”. While professional activity is regulated by national law in EU Member States, it is the UEMS’ understanding that it has to comply with international treaties and UN declarations on Human Rights as well as the World Medical Association (WMA) International Code of Medical Ethics (https://www.wma.net/policies-post/wma-internationalcode-of-medical-ethics).

This document derives from the previous Chapter 6 of the Training Charter and provides definitions of specialist competencies and procedures as well as how to document and assess them. For the sake of

transparency and coherence, it has been renamed as "Training Requirements for the Specialty of Medical Genetics". This document aims to provide the basic Training Requirements for the specialty and will be regularly updated in the future to reflect scientific and medical progress. The three-part structure of this document reflects the UEMS' approach to have a coherent pragmatic document not only for medical specialists but also for decision-makers at the National and European level interested in knowing more about medical specialist training.

The intention of this document is not to impose a European Curriculum but only to act as a guide for all Associations that wish to implement a European Curriculum at the national level.
UEMS is aware that there is still a wide variation in Medical Genetics training and professional profiles in Europe, and the aim of this document is to help the harmonisation of the different processes of Medical Genetics training in all countries whilst promoting the raising of standards across Europe. It is up to each National Association to adopt or adjust it to their national requirements.

Specialty of Medical Genetics

Medical Genetics is concerned with the identification, interpretation and communication of genetic factors that determine or influence disease development, as well as medical and personal management based on individual genetic information. This involves

- Understanding the relationship between genetic information (hereditary and somatic) and the normal function of the human body as well as the development of human diseases;
- Diagnosing genetic diseases and risk factors in the individual, clinically, functionally and through laboratory analyses;
- Assisting in the prevention and management of genetically caused diseases within interdisciplinary networks;
- Supporting individuals with genetic diseases, or risk factors, in their ability to deal with these conditions through genetic counselling and other measures.

The focus of Medical Genetics as a medical specialty is on recognising, understanding and explaining the link between the hereditary constitution (genotype) and the clinical manifestation (phenotype), whilst considering environmental, therapeutic and chance factors as well. Medical Genetics is important for all areas of medicine, with a particular focus on rare and undiagnosed diseases as well as multifactorial disorders with strong genetic factors such as inherited cancer predisposition syndromes.

The practice of Medical Genetics involves clinical and counselling services to individuals and families (and sometimes populations) with, or at risk of, genetic/hereditary diseases or other conditions, as well as medical services to medical and non-medical professionals. This includes the provision of diagnostic and genetic counselling services with information about the individual condition and its implications, such as management and follow-up, prognosis, screening, prevention and reproductive options, and therapeutic possibilities. This is based on thorough clinical assessment, family (pedigree) medical information, conventional laboratory investigations and imaging, and specialised genetic tests and their interpretation. Other components of Genetic Services include laboratory genetics (cytogenetics, molecular genetics and genomics, biochemical genetics, tumour genetics), specialised genetic counselling, and the provision of a knowledge and skills resource for all other medical disciplines, teaching and research. The core activities of Genetic Services can be defined as *integrated clinical, laboratory and counselling services provided for those with, or concerned about, a disorder with a significant genetic component (both inherited and sporadic)*. Due to the sharing of genes and DNA variation among family members, the whole family, not only the affected individual, can be considered the core patient in Medical Genetics. It is recognized that depending on national practice,

other medical specialties may provide genetic testing for a range of indications, including molecular pathology or pharmacology, in a variety of settings. Mutual respect and good interdisciplinary collaboration are at the core of medical genetic practice.

Medical Genetics is a rapidly developing specialty due to scientific advances in DNA sequencing technologies, but still includes many other cytogenomic approaches. The future of European Medical Genetics will depend on the equitable expansion of the specialty, the quality of training offered to trainees, and the resources to integrate advances in genomics into clinical care across all medical disciplines. This document relates to individuals with medical qualifications who seek to train in the specialty of Medical Genetics. It is recognised that there may be areas of overlap with training programmes for other genetic professionals (Clinical Laboratory Geneticists [non-medically trained scientists involved in laboratory diagnostics] as well as Genetic Counsellors) as well as other medical specialists such as molecular pathologists, and that there may be opportunities for periods of joint training during specialization.

Rare and undiagnosed diseases constitute an important area of expertise for Medical Geneticists as the large majority of these diseases have a genetic origin. Currently, it is estimated that for every 1,000 people, one new patient has a diagnosis of a rare disease per annum. Considering a caseload of about 100 rare disease patients / year for each Medical Geneticist, 1 Medical Geneticist per 100,000 persons in a population is required – and this relates only to the manpower needs for rare diseases. In view of the growing involvement of Medical Geneticists with common cancers (ovary, breast, colorectal), inherited cardiac conditions, fetal medicine teams (prenatal genetics) and assisted reproduction / preimplantation genetic diagnosis, and a growing complexity of investigations, the estimated manpower needs are 1 - 2 Medical Geneticists per 100,000 persons in a population. This figure may be significantly influenced by the availability of non-medical specialists in Medical Genetics, e.g. Genetic Counsellors.

The initial European Training Requirements (ETR) for Medical Genetics were endorsed by UEMS in 2017 and have now been revised. The new version has been prepared in 2021-2023 by the ETR Working Group of the Section of Medical Genetics under the lead of their Chair and the President of the Section. Major steps included, next to a general update,

- the collation of national training requirements in Medical Genetics, as far as available in English or understood by a member of the Working Group. This step was deemed necessary to gain more insight into the widely heterogeneous landscape of training requirements throughout Europe and was performed with student assistance. Medical Genetics is a specialty with a clinical and a laboratory part, and national differences concern in particular the weighting of laboratory skills.
- a completely new draft and later elaboration of the Syllabus, in order to give it a more convincing structure and, in particular, to align it to the content of the online textbook APOGeE. This is a freely available online textbook, emerging under the auspices of ERN ITHACA, the European Network for Rare Malformation Syndromes, in collaboration with the Section of Medical Genetics, and is meant to cover the complete knowledge to be achieved during training for Medical Genetics [Online Genetics Course APOGeE - ERN ITHACA (ern- ithaca.eu)]. The coordinator of ERN ITHACA and APOGeE is also a Delegate to the Section and member of the ETR Working Group.
- a fundamental revision of the description of the Specialty and its aims.
- the alignment of the ETR to the CanMEDS framework and to Competency Based Medical Education / Training.
- the inclusion of the European Examination to obtain the European Certificate in Medical Genetics and Genomics as summative assessment of the training.

Aims of Medical Genetics

The main aims of Medical Genetics can be summarized as follows, using the physician's role in the terms of the CanMEDS framework (http://canmeds.royalcollege.ca/en/tools) as guideline:

1. *Medical expert* for diseases and medical conditions that have or may have a genetic and/or hereditary basis: To provide a specialist service for the assessment, investigation, and diagnosis of such conditions in a resource-conscious and sustainable manner, interpretation of data, and to contribute to the management and treatment of affected individuals and families.
2. *Communicator:* To provide a service for information, counselling, education and support of individuals, couples or families with regard to diseases and medical conditions that are, or may be, genetic and/or hereditary. This often involves the interpretation of complex biological data.
3. *Collaborator:* To provide a knowledge and skills resource to all medical specialties and non-medical colleagues. This includes multidisciplinary and interprofessional meetings that are of particular importance in Medical Genetics.
4. *Health advocate:* To be an advocate, where necessary, of those affected by genetic and/or hereditary diseases and conditions, most of which are rare disorders, and to contribute to the public understanding of genetics and genomics, and their role in health and disease.
5. *Scholar:* To conduct and contribute to clinical and genomic research to enhance knowledge of all aspects with regard to diseases and medical conditions that are, or may be, genetic and/or hereditary, and to teach and instruct medical undergraduates and postgraduates as well as qualified physicians and non-physician colleagues in human and medical genetics and genomics.
6. *Leader:* To engage with others in providing a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinician, administrator, scholar, or teacher, fostering mutual understanding and respect in interdisciplinary and interprofessional teams.
7. *Professional:* To be committed to the well-being of individuals and the society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.

I. Training requirements for trainees

I.1 Trainees in Medical Genetics

Trainees in Medical Genetics are medical doctors who have completed their general professional training and are in an accredited training programme to become a recognised specialist in Medical Genetics. They are variably known in different countries as an intern, fellow or registrar in Medical/ Clinical/ Human Genetics.

I.2 Content of training and learning outcome

Physicians specialized in Medical Genetics need extensive knowledge and a wide range of clinical skills as genetic disorders can affect people of all ages and involve all body systems. They carry out both clinical and laboratory diagnostic professional tasks (often in close cooperation with Clinical Laboratory Geneticists) comprising the investigation, diagnosis, surveillance, treatment, prevention, and research into hereditary and somatic disorders caused by variation in the human genome. This includes the prediction of future health risk based on individual genetic data. The scope of patient care activities includes the recognition of variants, or variation, in the genome and the consequences for

pathophysiological processes, the early identification of individuals and families at risk, the identification of the genetic defect and the preventive care of affected family members, and prevention of intellectual and physical disability in those born with genetically-determined disorders, in addition to the rehabilitation of such patients. This includes referral of patients to other specialties within the context of multiprofessional interdisciplinary teams, e.g. of patients with problems in functioning to physical and rehabilitation medicine.

This specialty training is aimed at giving trainees competencies in the whole area of Medical Genetics to enable them to diagnose, treat, and counsel patients with genetic/hereditary diseases and their families in the light of current and expanding knowledge on the subject, with particular emphasis on understanding the molecular and cellular pathogenic mechanisms of such diseases.

Communication skills are particularly important in explaining complex concepts and genetic test results to families, in order to enable them to make informed decisions and choose appropriate course(s) of action. Medical Geneticists should be able to initiate, carry out to different degrees, and report genetic laboratory tests using all available relevant technologies in a wide range of settings, including diagnostic, carrier, and predictive testing, as well as periconceptional and prenatal testing. In some countries they are expected to run diagnostic genetic laboratories. Medical Geneticists should be able to perform genetic cascade and population screening for the early identification of individuals and families with an increased risk of common diseases with a strong inherited component. They also have an important role in public education and public debate about ethical, social, and other diverse issues that arise from new developments in the clinical application of genetic/genomic knowledge, particularly in relation to confidentiality, disclosure/non-disclosure of information, and beginning and end-of-life issues.

Medical Genetics is an interprofessional specialty that requires close and respectful collaboration of physicians with Clinical Laboratory Geneticists, Genetic Counsellors and Nurses, bioinformaticians, technical staff including engineers and artificial intelligence experts, as well as administrative and other staff. The spectrum of required competencies expected from Medical Geneticists differs between European countries, based on the establishment and acceptance of non-medicine specialties.

The content of the training and the learning outcomes, i.e. the statements of what a trainee knows, understands and is able to do on completion of the training process, are defined in terms of knowledge, skills and professionalism. It concerns areas of expertise depicted in I.2.1 and summarized below (I.2.2-1.2.4). Together, they are the competencies required of the trainee, which need to be assessed and documented (see I.3.3 and I.3.4).

I.2.1 General areas of expertise

- Medical Geneticists should have comprehensive clinical and laboratory diagnostic expertise with regard to a wide range of genetic and/or hereditary disorders, including:
    a. Structural developmental anomalies, e.g. malformations, and teratogenesis
    b. Neurodevelopmental disorders including intellectual disability
    c. Genetic acute and chronic dysfunction of all major organ systems in all age groups
    d. Genetic multi-system disorders in all age groups
    e. Genetic disorders affecting reproduction or manifesting in the pre- and perinatal period
    f. Genetic/hereditary tumour predisposition syndromes
- Medical Geneticists should be able to provide ad-hoc information, advice and support for specific hereditary and/or genetic conditions outlined in chapter 3 of the ETR syllabus.

I.2.2 Knowledge

A summary of the expected knowledge of a Medical Geneticist at the end of training follows. Details on the theoretical knowledge is provided in the syllabus in the appendix.

- Human Genetics and Genomics:
  - Basics of human genetics and genomics
  - Cell biology
  - Embryology and developmental genetics
  - Genomic variability and its functional consequences
  - Genetic laboratory analyses
- Medical Genetics
  - General aspects, e.g. clinical settings; ethical, societal, cultural, and legal aspects
  - Medical genetic consultations
  - Genetic testing
  - Management of genetic disorders
- Genetic (and in some cases Teratological) Basis of Human Disorders
  - Congenital morphological anomalies
  - Neurodevelopmental disorders
  - Neurological disorders
  - Epileptic disorders
  - Neuromuscular disorders
  - Psychiatric disorders
  - Ophthalmological disorders
  - Craniofacial anomalies and ear, nose, throat (otolaryngological) disorders
  - Dental disorders
  - Cardiac disorders
  - Multisystemic vascular disorders
  - Respiratory disorders
  - Hepatological disorders
  - Digestive and gastrointestinal disorders
  - Renal disorders
  - Urogenital and reproductive disorders
  - Dermatological disorders
  - Bone disorders and skeletal dysplasias
  - Endocrine disorders
  - Metabolic/biochemical genetic disorders
  - Connective tissue and musculoskeletal disorders
  - Immunodeficiency, autoinflammatory/autoimmune disorders
  - Haematological and coagulation disorders
  - Tumour predisposition syndromes

I.2.3 Clinical skills

A Medical Geneticist is expected to achieve the following clinical skills during her/ his training in Medical Genetics:

1. Interprofessional collaboration with Genetic Counsellors, nurses and other staff in a clinical genetics setting.

2. General clinical skills for a medical genetic consultation
    a. Take, record and interpret a detailed personal history and family history including the extraction of relevant information from medical reports and other relevant sources. Document the family pedigree with all relevant information according to standard guidelines.
    b. Carry out a comprehensive physical examination of all body systems, identify and describe morphological variants including dysmorphic features and malformations. Register phenotypic information using standard nomenclature (e.g. human phenotype ontology terms).
    c. Consult published articles, databases, textbooks, and other information resources relevant to the individual case.
    d. Summarize and interpret the available information and clinical findings with regard to a likely or potential genetic diagnosis and/or genetic risks.
    e. Identify and initiate appropriate genetic and non-genetic investigations and other measures. Select appropriate genetic laboratory tests from the whole range of available methods.
    f. Take and file informed consent, including consent for testing children, adults lacking capacity and individuals participating in research. Obtain and send appropriate samples.
    g. Document all activities in line with legal and ethical requirements.
    h. Highlight the implications for family members as appropriate.
3. General counselling skills for a medical genetic consultation
    a. Adhere to the principles of patient-centered communication based on individual circumstances and needs, using an approach of non-directiveness or shared decision making. Demonstrate awareness and sensitivity relating to the special issues of genetic diseases.
    b. Explain the genetic basis (pathogenesis, inheritance, variability, prognosis, etc.) of various types of disorders (monogenic, polygenic, multifactorial, etc.) to affected or at-risk individuals, parents and/or other relatives.
    c. Explain relevant genetic investigation with regard to purpose, nature, scope and significance, including potential results, limitations, and relevance for future management.
    d. Report and explain the results of genetic tests and their relevance for the individual.
    e. Assist and support individuals in making the best personal decisions for diagnosis, management of genetic disorders and reproductive planning.
    f. Explain the relevance of genetic findings with regard to other family members, and advise on resulting options and recommendations.
    g. Show the ability to adapt to particular consultation settings, such as predictive testing, prenatal testing, and counselling of minors and persons with reduced competence to consent.
    h. Demonstrate understanding of, and sensitivity to, different cultural, religious or social circumstances.
4. Interdisciplinary and interprofessional consultation skills
    a. Support and enhance collaboration with other medical professionals.
    b. Take an active role in a variety of clinical settings such as inpatient consultations or interdisciplinary case discussion (tumour patients, molecular tumour boards, fetal medicine, hereditary cardiac conditions etc.).
    c. Recognise the multiprofessional nature of Medical Genetics, interact with, respect and draw upon other professions as needed.

d. Provide detailed information on (potentially) genetic disorders with regard to likely diagnosis, differential diagnosis, investigations and management options.

5. Mutual and respectful collaboration with patient representatives and advocacy groups

I.2.4 Laboratory diagnostic skills

A Medical Geneticist is expected to achieve the following laboratory diagnostic skills during her/ his training in Medical Genetics:

1. Interprofessional collaboration with Clinical Laboratory Geneticists, technicians, bioinformaticians and other staff in a laboratory genetics setting.
2. Participate in a diagnostic genetic laboratory in the identification, characterization and interpretation of disease-related genetic (chromosomal, DNA, RNA) and epigenetic variants. Areas include:
   a. Sequence variants
   b. Structural and chromosomal variants
   c. Somatic non-tumour variants and mosaicism in different tissues
   d. Constitutional and somatic genetic variants in tumours
   e. Epigenetic and transcript variants
3. Assess the appropriateness of a requested laboratory genetic test with regard to:
   a. Indication and clinical question
   b. Limitations, and sensitivity/specificity
   c. Legal, ethical and professional issues
   d. Technical requirements such as sample, pre- and post-analytic handling, and storage.
4. Demonstrate familiarity with, and understanding of, the following laboratory methods, including sample management, laboratory procedures, bioinformatics and trouble shooting. In some countries this involves the ability to oversee or independently perform these methods:
   a. DNA/RNA extraction
   b. Cell culture, including lymphocytes, prenatal samples, and fibroblasts.
   c. Massively parallel sequencing (genome/exome/panel, short-read and long-read)
   d. Sanger Sequencing
   e. Variant-specific genotyping methods
   f. Repeat expansion analyses (fragment analysis, Southern blot etc.)
   g. Epigenetic analyses (bisulfite sequencing, methylation analysis etc.)
   h. Targeted quantitative analyses (MLPA, qPCR etc.)
   i. Gene expression analyses
   j. Classical chromosome analyses
   k. Fluorescence in-situ hybridization (FISH)
   l. DNA array for the detection of copy number variants
5. Describe identified variants, genotypes and karyotypes in standard nomenclature (HGVS for molecular genetics, ISCN for cytogenetics)
6. Determine the effects of genetic variants, using the whole range of available registries, databases, scientific publications, and other information sources:
   a. Gene variant effects on transcript and protein levels
   b. Genotype effects on clinical and other phenotypes
   c. Chromosomal variation effects on clinical and other phenotypes
   d. Pathogenicity classification of variants according to international systems and standards
7. Determine the relevance of identified variants for the specific clinical question in the investigated person and for family members.

8. Write a comprehensive report of the results of a genetic investigation, including indication, methodology, the relevance of the test result for the specific clinical question, and additional comments and/or recommendations for the tested person and family members as appropriate.
9. Explain genetic test results to non-genetic healthcare professional colleagues.
10. Initiate and carry out family-based analyses, including:
    a. Variant segregation analyses (both sequence and chromosomal variants)
    b. Linkage analyses
    c. Untargeted family analyses, such as trio (exome) analyses
11. Initiate and carry out analyses for specific indications, such as:
    a. Prenatal analyses and other methods in reproductive medicine as appropriate
    b. Predictive and carrier testing
    c. Polygenic score analyses
    d. Pharmacogenetic and/or pharmacogenomic analyses
12. Maintain awareness, and assess the relevance, of novel and emerging technologies in Medical Genetics.

I.2.5 Research

While research is important, and dedicated research training (clinical or laboratory based) is desirable in Medical Genetics, opportunities to undertake research will depend on local circumstances. Irrespective of whether such dedicated research training is available, a trainee is expected to achieve the following during training in Medical Genetics:

1. Identify relevant scientific research publications, critically assess their content, and understand the process of peer review of scientific work.
2. Understand the concepts and requirements of clinical and laboratory research studies, and understand how to write a research protocol, collect and analyse data using basic statistical methods.
3. Understand the phasing of clinical studies and the principles of good clinical practice.
4. Participate in research related to Medical Genetics, e.g. in the following areas:
    a. Genetic basis of human diseases, including the clinical effects of genetic variants
    b. Natural history, variability and prognosis of genetic disorders
    c. Treatment of genetic disorders, clinical trials
5. Present scholarly work at least once at a national or international conference, and to have at least one peer-reviewed publication under supervision, ideally as first or last author, or with authorship demonstrating a significant contribution to the design, execution and analysis of the study, as well as drafting or revising the paper.
6. Maintain or contribute to genetic databases and biobanks.

I.2.6 Teaching and training

1. Participate in pre- and postgraduate teaching in medicine, laboratory genetics and genetic counselling.
2. Participate in teaching and training of persons in technical and non-academic professions.
3. Participate in public education activities.

I.2.7 Non-technical skills and professionalism

Medical Geneticists – like all physicians – have a strong responsibility for the well-being and benefit of others and the society. This should be demonstrated in all professional activities including reflective thinking and communication, decision making, and risk taking. Beyond the required mastery of the art,

science, and practice of their specialty, Medical Geneticists must show clinical competence, humility, a commitment to ongoing professional development, and promotion of healthcare justice and the public good. They must adhere to ethical standards, and be role models in values such as integrity, honesty, altruism, humility, respect for diversity, and transparency with respect to potential conflicts of interest. In order to provide the best possible medical service they must also care for their own health and well-being and that of their colleagues. Medical Geneticists – like all physicians – are accountable to those served, to society, to their profession, and to themselves. Specific aspects include:

1. Respect and compassion towards individuals with medical needs
2. Respect towards medical and non-medical colleagues and junior staff
3. Abide by the values of honesty and confidentiality
4. Maintain competence throughout their career
5. Improve care by evaluating its processes and outcomes
6. Participate in educational programmes
7. Safeguard the rights of the vulnerable
8. Provide care irrespective of age, gender, race, disability, religion, social or financial status
9. Deliver best quality care in a compassionate and caring way

I.2.8 Levels of Competence

As training progresses, the trainee should have the opportunity for increasing autonomy, consistent with safe and effective patient care. The national training programme should establish a realistic timetable for development of competencies that are expected as part of training in Medical Genetics, beginning with observation, continuing with supervised clinical care, and ultimately reaching a level of knowledge, skills and professionalism that are judged to be sufficient for specialised, independent practice.

It is recommended that competencies are defined according to the concept of *Entrustable Professional Activities* (EPAs) based on specific units of clinical and laboratory work. The ability to carry out a competent independent medical genetic consultation is one of the core functions that a medical genetic specialist must be able to perform. At the beginning of training, trainees observe different trainers in various consultations. They subsequently take over functions of an *assistant*, carrying out specific tasks under direct supervision. This period should be completed with documented assessment of competencies required for a simple consultation. In the second phase, trainees perform a consultation under supervision, carrying out a consultation from start to finish with the trainer available for immediate advice and intervention when necessary. The trainer joins the counsultation e.g. at the end to make sure that all relevant points have been addressed, and the counselees do not have remaining open questions. Assessment of competencies after this period involves knowledge of personal limitations and when to call for assistance or advice from the supervisor. In the third phase, the trainee carries out consultation under indirect supervision, with the trainer available but not in direct contact with the trainee. Assessment of competencies at the conclusion of this period involves the ability to assess and adapt to well-known variations, and to solve problems with advice from the trainer. In the fourth phase, the trainee carries out the majority of consultations without assistance and only requires occasional help or advice. At the completion of the fifth and final phase, the trainee is able to deal with straightforward and difficult cases to a satisfactory level and without the requirement for external input, and is capable of instructing and supervising trainees. The key factor in the EPA concept is entrustment: the trainee is not only capable of tackling the particular procedures or units independently, but can be trusted to do this by his tutors. The EPA concept should be developed for different essential and desirable consultation settings as well as other core activities expected from Medical Geneticists throughout Europe. 5th level of competencies should be included in a standardised logbook template for all trainees in the future, based on national requirements. Harmonisation of competencies, and their level at different points of the training, expected from trainees in Medical

Genetics in different countries requires however extensive ongoing consultation.

I.3 Organization of training

I.3.1 Schedule of training

The optimal Medical Genetics training is 4 years full time training in a Medical Genetics Centre in an accredited programme. This should be preceded by at least 1 year of general training (common trunk), covering medicine and paediatrics if possible, and separate from the 4 year specialist training. The key purpose of this is the acquisition of core clinical competencies after graduating from medical school. Depending on national regulations, the training may start immediately after completion of medical school.

Optimal training would be:

- 1 year (or more) common medical trunk training including some of the following: general practice, paediatrics, obstetrics and gynaecology, neurology and psychiatry, internal medicine.
- 4 years Medical Genetics practice, with at least 2 years' time working in patient care in Medical Genetics and at least 6 months working in genetic laboratory diagnostics.
- If the candidate already had a board exam in a clinical specialty, repetition of the 1 year common trunk is not necessary.

I.3.2 Curriculum of training

Because of the divers health systems and clinical settings, as well as the variable spectrum of skills required from Medical Geneticists in different European countries, defining a standard European curriculum is challenging. In most countries the primary focus is on developing knowledge and skills for medical genetic consultations. This requires intensive preparation of submitted clinical information on scheduled cases as well as thorough work-up after patient contact. In most training centres there are weekly case conferences and clinical-ethical discussions which also serve as teaching opportunities. Writing concise clinical summaries to medical colleagues as well as individual consultation letters in plain language to patients under the supervision of trainers is an important learning experience. Similarly in the laboratory diagnostic areas, carrying out and/or interpreting numerous genetic analyses and writing comprehensive but concise reports under expert supervision is fundamental for learning to understand genotype-phenotype correlations, which are at the heart of understanding medical genetics. After the first years of training, the focus usually shifts to different specializations in medical genetics which foster in-depth knowledge for specific rare diseases. Interdisciplinary contacts with other medical specialties foster bidirectional transfer of knowledge and expertise and support understanding for the different points of view. Finally, participation in conferences and workshops is an important training element in a rapidly moving specialty.

I.3.3 Documentation of training

Each trainee should keep an official national trainee logbook/portfolio. In this logbook the trainee demonstrates that he/she has been sufficiently exposed to and dealt with a wide range of medical genetic cases in clinics and laboratories. Logbooks should be monitored regularly and undersigned by the trainee and the Training Programme Director or the designated staff member. The content of a logbook/portfolio depends on the requirements of the particular country and should optimally include:

- information on training posts, dates, duration of training and trainers
- competence-based list of performed consultations in the following areas:
  - prenatal genetic diagnoses

  - reproductive disorders and differences of sex development
  - congenital morphological anomalies and syndromes
  - neurodevelopmental disorders
  - neurologic, neuromuscular and psychiatric disorders, epilepsies
  - ophthalmological disorders
  - craniofacial anomalies and ear, nose, throat disorders, dental disorders
  - disorders of heart and vessels
  - respiratory, liver and gastrointestinal disorders
  - renal and urinary tract disorders
  - disorders of skin and connective tissue
  - skeletal and growth disorders
  - metabolic disorders
  - endocrine disorders
  - immunodeficiency and autoinflammatory/autoimmune disorders
  - haematological and coagulation disorders
  - tumours and tumour predisposition syndromes
  - pharmacogenetics
- competence-based list of performed laboratory investigations in the following areas:
  - diagnostic (molecular) cytogenetic analyses
  - diagnostic molecular genetic analyses (including imprinting disorders)
  - clinical genome analyses
- list of internal and external courses attended
- list of publications
- list of research/clinical presentations at a local, regional, national or international meeting
- list of institutional mandatory training courses completed, including all aspects of safeguarding

I.3.4 Assessment and evaluation

All aspects of training should be appropriately supervised and assessed. Assessment of competencies is a process by which information is obtained relative to a known training objective or goal, and is a broad term that includes but is not restricted to testing. Assessment of trainees should include summative and formative elements. Formative assessment follows defined criteria in a defined period, and a summative assessment addresses the candidate's achievement at the conclusion of a defined period or project. Assessment by the Training Programme Director or the trainers, i.e. members of the staff designated for this task, should be done on a regular basis. A wide range of tools (knowledge tests, clinical examinations, in-training assessments) is available to assess progress in the levels of independence required for each competence of the curriculum. These should be used routinely as part of the learning process with timely and specific feedback on performance. Trainees should document frequent workplace-based assessments throughout training to allow them to gather evidence of competence, receive feedback and continually gain autonomy in their professional practice. A logbook (see 1.3.3 for content) is strongly recommended and has already been adopted by many countries as part of a system for regular monitoring of trainees' progress. Some have annual appraisals including tests of knowledge, whilst others do not. Similarly, most countries hold validated examinations at the end of training, which form one part of the assessment for certification, whilst a minority do not. Formative appraisal, in particular, allows individual deficiencies to be addressed in a timely manner without prolonging the overall training time, or prolonging it minimally. It also allows Quality Assurance of the Training Centres and Trainers. National Associations and Training Authorities are tasked with developing appraisal systems, and individual training centres with the development of an assessment framework that ensures effective progression in reaching the required competencies. The level of supervision should be appropriate for the documented competence of the trainee and the clinical

situation, it should also routinely include the opportunity to personally discuss all cases.
A final, end-of-training examination is an effective tool for defining the competence of a physician trained in Medical Genetics. It should assess overall competence and therefore cover the whole curriculum. The final examination ideally comprises a written paper, usually in MCQ format, which tests the candidates' knowledge, and a separate oral examination, which evaluates clinical skills, related competencies, and some aspects of professional behaviour. It should be emphasized that successful completion of a final examination does not confer Specialist status on its own but will be one of the concluding steps in a training programme where all other steps have been fulfilled successfully.
The final examination can be provided at a national level following the rules of the National Regulatory Authority in each European country that also stipulates the other parts of the training system before a trainee is recognized as a Specialist.
The final examination can also be the European Examination to obtain the European Certificate in Medical Genetics and Genomics (ECMGG). The ECMGG examination is intended to be the main knowledge-based assessment tool for Clinical/Medical Genetics and Genomics training across Europe and also tests some skills, competencies and attitudes, establishing world class-leading standards in the specialty throughout all European countries. At present the ECMGG examination comprises two parts, taken separately online, with the written section sat in April, and the oral examination taken in June. The examination is currently in English only. Ideally it should take place towards the end of training, usually in the final year, or close to obtaining the national certification. Further information can be found at www.uems-ecmgg.org.
The ECMGG examination is still young and had its inauguration in 2019. The current online format was introduced after a break caused by the Coronavirus pandemic in 2021. The examination has been CESMA appraised for its content, and a full CESMA appraisal including all organisational processes will be applied for in relation to the ECMGG examination in 2024. While the ECMGG examination is not to be considered as a formal qualification, it is a high-standard examination, has performed extremely well using accepted statistical methods, and its renown has increased over the past few years. As a result, the first countries have recognized the ECMGG examination as part of, or equivalent to, their national examination, or it is officially recommended.

I.3.5 Governance

The governance of an individual's training programme will be the responsibility of the Programme or Course Director and the institution(s) in which the training programme is being delivered. A trainer (who will have satisfied the requirements laid out below, Section II) will be responsible to the Programme Director for delivering the required training in their area of practice. The governance of the ECMGG examination is the responsibility of the UEMS Section of Medical Genetics and the European Board of Medical Genetics, Branch of Medical Geneticists, and is also observed by representative(s) of the European Society of Human Genetics.

II. Training requirements for trainers

II.1 Process for recognition as trainer

II.1.1 Requested qualification and experience

Trainers should be certified Medical Geneticists and must be recognised by the national authority. Trainers should provide evidence of academic activities (clinical and/or basic research, publications in peer reviewed journals, and participations in medical genetic scientific meetings) and professional

experience. They should possess the necessary administrative, communicative, teaching and clinical skills and commitment to conduct the programme. Trainers and Training Programme Directors must be in active clinical practice and engaged in training in the training centre. The Training Programme Director will usually be a certified specialist for a minimum of 5 years. He/she organizes the activities of the educational programme in all institutions that participate in the programme.

II.1.2 Core competencies for trainers

1. Familiar with all aspects of Medical Genetics.
2. Experienced in teaching and in supporting learners.
3. Skilled in identifying the learning needs of the trainees and in guiding the trainees to achieve their educational and clinical goals.
4. Trained in the principles and practice of medical education and follow regular updating in educational and team leader skills.
5. Ideally act as a lecturer to a peer-audience on a regular basis, attend national or international meetings, and able to demonstrate appropriate participation in continuing professional development.
6. Able to recognise trainees whose professional behaviour is unsatisfactory and initiate corrective and supportive measures as needed.
7. Have leadership skills to guide the trainee.

II.2 Quality management for trainers

Trainers and Training Programme Directors will have their job description agreed with their employer which will allow them sufficient time for support of trainees. Feedback from trainees is necessary for optimal training.

As it belongs to the core competencies for trainers to be trained in medical education and to update educational and team leader skills regularly, it is important that trainers are offered regularly the opportunity for training for this purpose.

The educational work of trainers and Training Programme Directors should be appraised not less than on annual basis within their Institution as local circumstances determines.

III. Training requirements for training institutions

III.1 Process for recognition as training centre

III.1.1 Requirement on staff and clinical activities

A training centre is a place, or number of places, where trainees are able to develop their Medical Genetics competencies. Thus, training may take place in a single institution, or in a network of institutions working together, to provide training in the full spectrum of clinical conditions and skills detailed in the curriculum. A training institution must have national accreditation, in agreement with UEMS standards, and should possess an adequate infrastructure to offer qualitative and quantitative clinical exposure, and to provide adequate supervision, learning materials, dedicated time for learning, and structured assessments.

Each participating institution in a network must be individually recognised as a provider of a defined section of the curriculum. Training centres must have a sufficient throughput of patients, an appropriate case-mix to meet training objectives, and be adequately resourced with teaching staff. The training must expose the trainee to a broad range of clinical experience.

The training of a trainee will be led and managed by a specialist. This specialist will be active in the practice, with personal responsibility for the management of patients with a wide range of genetic conditions. Within a training centre there should be a team of specialists, each with subspecialty expertise and able to supervise and train a trainee. Allied specialties should be present to a sufficient extent to provide the trainee with the opportunity of developing his/her skills in a multidisciplinary approach to patient care and to ensure the represenation of domain specialists in multidisciplinary teams. There is no specific trainee/trainer ratio required, but there should be a minimum of two teachers in a training centre, and it is likely that non-medical healthcare professionals will also be engaged. Trainees should have adequate peer support, ideally in the form of at least one other trainee in Medical Genetics. Trainees may also benefit from having a mentor who is independent of the department in which they train.

The trainee should be involved in the diagnosis and management process of new patients (out- patients and in-patients), as well as their follow up. A trainee must demonstrate increasing personal responsibility for the global care of patients with genetic conditions. There should be written general guidelines within the training institution concerning patient care and patient information (including informed consent), referrals, medical records, documentation, on-call and back-up schedules, attendance at conferences and educational/training courses.

Each centre should undergo structured monitoring by the relevant authority including surveys and external evaluation of training and assessment at least every five years. The staff of a training centre should also engage collaboratively in regular internal reviews and audit of the centre's clinical activity and performance. The internal system of quality assurance should include structured reporting of clinically relevant errors.

There should be regular multi-disciplinary meetings to determine optimal care for patients, involving both medical and other healthcare professionals. There will be clinical engagement beyond the centre with other clinical groups such as Cardiology, Dermatology, Neurology, Obstetrics and Gynaecology, Oncology, Ophthalmology, Orthopaedics, Paediatrics, Surgery, and other specialties, as well as other diagnostic groups, especially pathology, laboratory medicine and radiology.

Specialist staff appointed to a training centre will have completed all training requirements themselves and will have been trained also in teaching and mentoring trainee staff, as well as in working in a multidisciplinary team with lab and Genetic Counsellors (see Section II).

III.1.2 Requirement on equipment, accommodation

A training centre should have sufficient equipment and support to enable the clinical practice that would be expected of a training centre and thus provide the necessary educational opportunities for trainees.

Training institutions should have a library and internet facilities offering access to the current world scientific literature, including major international Medical Genetics journals, and should provide the necessary physical infrastructure for trainees including conference nuclear rooms and allocated office space with computer access.

Research is fundamental to the practice of Medical Genetics, as described in the CanMEDS framework in the role of a Medical Geneticist as a "scholar". Trainees must acquire the skills to critically evaluate new research and its implications for clinical practice. They should also acquire a detailed understanding of the design and conduct of basic, translational, clinical and epidemiological research either in their training institution or in collaboration with other centres or universities. Training programmes should provide sufficient flexibility to allow periods of full-time or part-time research with appropriate adjustment of the total training time.

III.2 Quality Management within Training Institutions

Participation of the training institution in a certified quality management programme with an external auditing process on a regular basis is consistent with good governance. Criteria of quality management at specialty training institutions include the following:

III.2.1 Accreditation

Training institutions need to be accredited with competent National Medical Boards.

A training institution must have an internal system of medical audit or quality assurance. Quality assurance must be an integral part of the training programme of all training institutions/networks. A national register of approved institutions/networks should be available.

Internal regulations: There should be written general guidelines within the training institution concerning patient care and patient information (including informed consent), referrals, medical records, documentation, leave (annual, study), maternity/paternity, residents' working schedules, attendance to conferences and to educational activities. These should be available to staff and trainees.

III.2.2 Clinical governance

The governance of a training programme is the responsibility of the Programme Director and the institution(s) in which the training programme is being delivered. A trainer will be responsible to the Programme Director for delivering the required training in his/her area of practice.

Employee-structure at training institutions needs to be designed in a way to accommodate for specialty training. Workload has to be managed with a priority on training.

III.2.3 Manpower planning

Training institutions should appoint a coordinator responsible for the composition, implementation and supervision of a specialty training programme. Roles of trainer and trainee need to be clearly defined. Allotted sessional time should be scheduled frequently and regularly for specialty training interaction. The precise time allocation will depend on local structures and resources.

Manpower planning is under jurisdiction of each member state according to their needs for Medical Genetics specialists.

III.2.4 Regular report

Annual reports on various aspects of an institution's specialty training programme should be made publicly available.

III.2.5 External audit

Training institutions should appoint a coordinator who is also responsible for compliance of the training programme with current guidelines, directives or regulations of competent medical boards, as well as the local medical school.

III.2.6 Transparency of training programmes

Based on national and regional guidelines, UEMS strongly encourages training institutions to formulate defined training programmes and make them publicly available (e.g. on their website). It would be expected that a training centre would publish details of the training provision available with details of the clinical service it provides and the trainers. Such information would include the training programmes, the nature of the clinical or laboratory experiences in which a trainee would be engaged, and the support and interaction with the trainer and Programme Director. There would be a named individual whom a prospective trainee might contact and discuss the programme.

III.2.7 Framework of approval

The content of training programmes should also make clear how, and by whom, key achievements of training will be ascertained leading to a higher level of clinical responsibility and new assignments.
To assist a European medical specialist with additional Medical Genetics competence moving from one European country to another it would be expected that they have satisfactorily completed a training programme. After the examination in Medical Genetics they may be able to demonstrate that he/she has the required knowledge, clinical and laboratory skills and competencies, as well as having demonstrated appropriate professional behaviours. Such accomplishments would be verified both by relevant documents and by the testimony of trainers and other staff who have worked with the trainee.

III.2.8 Feedback from trainers and trainees

Feedback about programme quality from both trainers and trainees must be systematically sought, analysed and acted upon. Trainers and trainees should be actively involved in using its results for programme improvement and development.

Contributions

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Review

The final draft of the ETR for Medical Genetics has been reviewed for the European Society of Human Genetics (ESHG) by William Newman (UK; President-Elect and Chair Education Committee ESHG) and Edward Tobias (UK; member Education Committee ESHG), and for the European Board of Medical Genetics (EBMG) by Birgitte Diness (Denmark; Past President EBMG) and Thomas Liehr (Germany; Chair Branch of Clinical Laboratory Geneticists of the EBMG).

Acknowledgements

We want to express our grateful thanks to Siobhan Kerr, student assistant, University of Dundee, who collated and analysed existing national training requirements.

European Training Requirements for the Specialty of Medical Genetics: Appendix

European Standards of Postgraduate Medical Specialist Training

Syllabus

1	***Human Genetics and Genomics***
1.1	***Background and general aspects***
	Introduction. General aspects: Genetics and Medicine. The concept of rare diseases. Historical aspects. Terminology
1.2	***Basics of Human Genetics and Genomics***
1.2.1	Genome
1.2.1.1	General concepts
1.2.1.2	Genome organisation overview (nucleosome, domains, compartments, etc.)
1.2.1.3	Nucleic acids: DNA and RNA
1.2.1.4	Chromosomes
1.2.1.5	Mitochondrial genome
1.2.2	Genes
1.2.2.1	Protein-coding genes: structure and function
1.2.2.2	Non-protein-coding genes
1.2.3	Gene regulation and epigenetics
1.2.3.1	Concepts
1.2.3.2	Histone and DNA modifications, Chromatin configuration
1.2.3.3	Imprinting
1.2.3.4	Transcription and transcription regulation
1.2.3.5	Transcription factor families (Homeobox, Paired Box/PAX, Forkhead, T-Box, SOX, others)
1.2.4	Translation and post-translational processing
1.2.4.1	Ribosomes
1.2.4.2	Translation and translation regulation
1.2.4.3	Post-translational processing and control
1.3	***Cell biology***
1.3.1	Cells and organelles
1.3.1.1	Cytoskeleton
1.3.1.2	Mitochondria
1.3.1.3	Peroxisomes
1.3.1.4	Lysosomes
1.3.1.5	Endoplasmic reticulum and Golgi apparatus
1.3.1.6	Other organelles
1.3.1.7	Intracellular trafficking
1.3.2	Cell membrane
1.3.2.1	Junctions
1.3.2.2	Transporters

1.3.2.3	Channels
1.3.2.4	Receptors
1.3.2.5	Cilia (primary, motile)
1.3.3	Major signalling pathways
	SHH, Wnt, TGF-b, FGF, GDNF, RTK/RAS/MAP & PI3K/AKT, EPHRIN, TNF, NOG, MYC, Notch, p53, GNBP
1.3.4	Extracellular matrix
	Fibres, cells, matrix, function
1.3.5	Cell cycle and cell division
1.3.5.1	Cell cycle, mitosis
1.3.5.2	Meiosis, gametogenesis
1.3.6	Mutagenesis, genome maintenance and cell death
1.3.6.1	Mutagenesis
1.3.6.2	DNA repair
1.3.6.3	Cell death, apoptosis
1.4	***Embryology and developmental genetics***
1.4.1	Early embryonic development
	Sex determination, neural crest, neural tube, left-right asymmetry, somites, craniofacial development
1.4.2	Twinning
1.4.3	Organ development
1.4.3.1	Brain and sensory organs (eyes, ears, smell)
1.4.3.2	Peripheral nervous system and muscle
1.4.3.3	Bone and cartilage, limbs
1.4.3.4	Heart and blood vessels
1.4.3.5	Renal and urogenital system
1.4.3.6	Endodermal derivatives: lung, liver, pancreas, gut
1.4.3.7	Skin and epidermal appendages: teeth, hair
1.4.3.8	Endocrine organs
1.4.3.9	Blood and immune system
1.4.4	Postnatal development and aging
1.4.4.1	Child and adolescent development
1.4.4.2	Aging
1.5	***Genomic Variability and Its Functional Consequences***
1.5.1	Genetic and genomic variability
1.5.1.1	Sequence variants
1.5.1.2	Structural variants
1.5.1.3	Epigenetic variants, uniparental disomy (UPD)
1.5.1.4	mtDNA variants
1.5.2	Functional variant effects
1.5.2.1	Quantitative variant effects
1.5.2.2	Qualitative variant effects
1.5.2.3	Complex variant effects
1.5.3	From genotype to phenotype
1.5.3.1	Major concepts
1.5.3.2	Dominance/recessiveness
1.5.3.3	Penetrance/expressivity, epistasis etc.
1.5.4	Inheritance modes

1.5.4.1	Monogenic inheritance (autosomal dominant, autosomal recessive, X-chromosomal, Y-chromosomal, mitochondrial)
1.5.4.2	Digenic inheritance
1.5.4.3	Multifactorial and complex disorders
1.5.5	Mosaicism
1.5.5.1	General principles
1.5.5.2	Specific aspects of mosaicism
1.5.6	Tumour genetics
1.5.6.1	Genetic basis of tumour development
1.5.6.2	Oncogenes
1.5.6.3	Tumour suppressor genes
1.5.6.4	Clonal haematopoiesis of indeterminate potential (CHIP)
1.5.6	Genetics at a population level
1.5.6.1	Principles of population genetics
1.5.6.2	Hardy-Weinberg equilibrium
1.5.6.3	Linkage analysis
1.5.6.4	Association studies
1.5.6.5	Genetic epidemiology
1.6	***Genetic Laboratory Analyses***
1.6.1	Cytogenetic analyses
1.6.1.1	Classical chromosome analysis (banding cytogenetics)
1.6.1.2	Fluorescence in-situ hybridisation (FISH)
1.6.1.3	Chromosomal microarray
1.6.1.4	Chromosomal variant nomenclature (ISCN)
1.6.2	Molecular genetic analyses
1.6.2.1	PCR-based sequence analysis
1.6.2.2	Quantitative analyses (qPCR, ddPCR, MLPA)
1.6.2.3	Repeat expansion analysis (fragment analysis, Southern blot)
1.6.2.4	Massive-parallel sequencing
1.6.2.5	Methylation analysis, epigenomics, other modifications
1.6.2.6	Transcriptomics
1.6.2.7	Molecular variant nomenclature
1.6.3	Tumour genetic analyses
1.6.3.1	Tumour analysis: General considerations
1.6.3.2	Tumour cytogenetics
1.6.3.3	Tumour sequence analysis
1.6.3.4	Liquid biopsy
1.6.4	Bioinformatics
1.6.4.1	Databases
1.6.4.2	Web resources
1.6.4.3	Methods for causative gene identification
1.6.5	Proteomics and biochemical genetics
1.6.5.1	Proteomics
1.6.5.2	Important biochemical tests
1.6.5.3	Metabolomics, lipidomics
1.4.3	Experimental biology
1.4.3.1	Genome editing
1.4.3.2	Model systems

2	**Medical Genetics**
2.1	***General aspects***
2.1.1	Settings
2.1.1.1	Inpatient and outpatient consultations
2.1.1.2	Interprofessional teams in medical genetics
2.1.1.3	Patient representatives and self-help structures
2.1.1.4	Interdisciplinary collaboration and boards
2.1.1.5	Registers and biobanks
2.1.1.6	IT resources, expert systems
2.1.2	Clinical research in Medical Genetics
2.1.3	Ethical, societal, cultural, and legal aspects
2.1.3.1	Ethical aspects
2.1.3.2	Societal and cultural aspects
2.1.3.3	Genetic legislation and regulatory aspects, accreditation
2.1.3.4	National, European and international network structures, CPMS, ERNs
2.1.3.5	Data Protection
2.1.3.6	Reproductive legislation
2.1.3.7	Consumer genetics
2.1.4	Personalized genetic and genomic medicine
2.1.5	Genetics on the web
2.2	***Medical genetic consultations***
2.2.1	Genetic diagnosis
2.2.1.1	Personal history
2.2.1.2	Family history
2.2.1.3	Clinical/morphological examination
2.2.2	Probability calculation and statistics
2.2.2.1	Probability theory
2.2.2.2	Bayes‘ theorem
2.2.3	Genetic counselling
2.2.3.1	Genetic counselling and communication
2.2.3.2	Concepts pre/post genetic counselling
2.3	***Genetic testing***
2.3.1	Indications for genetic/genomic tests
2.3.2	Postnatal Genetic Testing
2.3.2.1	Indications
2.3.2.2	Diagnostic testing
2.3.2.3	Presymptomatic and predictive testing
2.3.3	Prenatal Genetic testing
2.3.3.1	Preimplantation testing
2.3.3.2	Diagnosis by prenatal imaging
2.3.3.3	Non-invasive prenatal testing (NIPT)
2.3.3.4	Prenatal sampling and testing
2.3.3.5	Legal aspects
2.3.3.6	Ethical aspects
2.3.4	Genetic screening
2.3.4.1	Newborn screening

2.3.4.2	Population screening
2.3.4.3	Carrier testing
2.3.5	Specific clinical situations
2.3.5.1	The critical ill patient
2.3.5.2	The patient with a multi-system disease
2.3.6	Pharmacogenetics and -genomics
2.3.6.1	Pharmacogenetics and adverse drug reactions (ADR)
2.3.6.2	Pharmacogenomics
2.4	***Management of Genetic Disorders***
2.4.1	General management aspects
2.4.2	Non-specific phenotype-targeting treatments
2.4.3	Gene therapy
2.4.4	Gene editing
2.4.5	RNA targeting
2.4.5.1	Action on gene transcription
2.4.5.2	Action on splicing
2.4.5.3	Action on translation
2.4.6	Protein-based therapy
2.4.6.1	Therapeutics targeting abnormal protein
2.4.6.2	Indirect pharmacological therapies
2.4.6.3	Protein replacement & enzymotherapies
2.4.2.4	Cell therapy
2.5	***General Skills***
2.5.1	Medical skills
2.5.1.1	Taking blood and tissue samples
2.5.1.2	Infection control
2.5.1.3	Medical documentation, photography
2.5.2	Management skills
2.5.2.1	Time management
2.5.2.2	Ancillary competences

3	**Genetic Basis of Human Disorders**
3.1	***Congenital morphological anomalies***
3.1.1	Dysmorphism (morphological variants)
3.1.2	Major morphological anomalies
3.1.2.1	Classification, pathogenetic mechanisms (malformation, deformation, disruption, dysplasia)
3.1.2.2	Epidemiology
3.1.2.3	Common malformations (see disease groups)
3.1.2.4	Malformation sequences (incl. Moebius)
3.1.2.5	Malformation associations (incl. VACTERL, MURCS)
3.1.3	Clinical approach to a child with multiple congenital anomalies
3.1.4	Common syndromes with multiple congenital anomalies
3.1.4.1	Autosomal trisomies and microscopically visible chromosomal syndromes
3.1.4.1.1	Down syndrome (trisomy 21)
3.1.4.1.2	Edwards syndrome (trisomy 18)

3.1.4.1.3	Pätau syndrome (trisomy 13)
3.1.4.1.4	Wolf-Hirschhorn syndrome ($4p^-$)
3.1.4.1.5	Cri-du-chat syndrome ($5p^-$)
3.1.4.1.6	Pallister-Killian syndrome (mosaic isochromosome 12p)
3.1.4.2	Microdeletion and -duplication syndromes
3.1.4.2.1	7q11.23 (Williams syndrome)
3.1.4.2.2	15q-associated microdeletion syndromes (incl. 15q13.3)
3.1.4.2.3	16p11.2 (deletion; duplication)
3.1.4.2.4	17p11.2 (Smith-Magenis syndrome, Potocki-Lupski syndrome)
3.1.4.2.5	17p13.3 (Miller-Dieker syndrome)
3.1.4.2.6	22q11.2 (DiGeorge/Shprintzen/VCF syndrome; duplication)
3.1.4.2.7	22q13 (Phelan-McDermid syndrome)
3.1.4.3	RASopathies
3.1.4.3.1	Noonan syndrome
3.1.4.3.2	Other RASopathies (CFC syndrome, Costello syndrome, Legius syndrome)
3.1.4.4	PI3K/AKT dysregulation disorders
3.1.4.4.1	Proteus syndrome
3.1.4.4.2	*PIK3CA*-related overgrowth spectrum
3.1.4.5	Chromatinopathies
3.1.4.5.1	Cornelia de Lange syndrome
3.1.4.5.2	Coffin-Siris syndrome
3.1.4.5.3	Nicolaides-Baraitser syndrome
3.1.4.5.4	Kabuki syndrome
3.1.4.5.5	CHARGE syndrome
3.1.4.5.6	Rubinstein-Taybi syndrome
3.1.4.5.7	Kleefstra syndrome
3.1.4.5.8	Smith-Magenis syndrome
3.1.4.5.9	Sotos syndrome
3.1.4.5.10	Seckel syndrome
3.1.4.6	Disorders with limb defect as major feature
3.1.4.6.1	Holt-Oram & Ulnar-Mammary syndromes
3.1.4.6.2	Thrombocytopenia-absent radius syndrome (TAR) syndrome
3.1.4.6.3	Townes-Brocks syndrome
3.1.4.6.4	Feingold syndrome
3.1.4.6.5	Ectrodactyly, ectodermal dysplasia and cleft lip and/or palate (EEC) syndrome
3.1.4.7	Disorders with craniofacial anomalies as major feature
3.1.4.7.1	Frontonasal Dysplasia
3.1.4.7.2	Craniofrontonasal syndrome
3.1.4.7.3	Treacher-Collins syndrome
3.1.4.7.4	Hemifacial Microsomia (Goldenhar syndrome)
3.1.4.8	Other monogenic syndromes
3.1.4.8.1	Notch pathway disorders (Alagille syndrome, spondylocostal dysostosis)
3.1.4.8.2	Homeobox gene disorders (Currarino triad)
3.1.4.8.3	Sonic hedgehog pathway (Pallister-Hall-, Greig syndrome)
3.1.4.8.4	Aarskog syndrome
3.1.4.8.5	Berardinelli-Seip Congenital Lipodystrophy
3.1.4.8.6	Mowat-Wilson syndrome
3.1.4.8.7	Waardenburg syndrome
3.1.4.8.8	Miscellaneous syndromes (KBG syndrome, Simpson-Golabi-Behmel syndrome)

3.1.4.9	Imprinting disorders
3.1.4.9.1	Prader-Willi syndrome
3.1.4.9.2	Maternal UPD 14
3.1.4.9.3	Silver-Russell syndrome
3.1.4.9.4	Beckwith-Wiedemann syndrome
3.1.5	Teratogenesis
3.1.5.1	Fetal alcohol syndrome and other drugs (e.g. cocaine)
3.1.5.2	Medications (retinoids, antiepileptics [hydantoine, valproate], warfarin, ACE inhibitors, lithium, fluconazole, thalidomide)
3.1.5.3	Maternal diseases (PKU, diabetes)
3.1.5.4	Infections (rubella, toxoplasmosis, CMV, Herpes Virus 1, HSV 2, Zika, HIV)
3.1.5.5	Irradiation
3.2	***Neurodevelopmental disorders (NDD)***
3.2.1	Neurodevelopmental anomalies: overview
3.2.2	Intellectual disability and NDD: evaluation and diagnostic strategies
3.2.3	Syndromes with intellectual disability & NDD
3.2.3.1	X-linked intellectual disability syndromes
3.2.3.1.1	Fragile X syndrome
3.2.3.1.2	Rett syndrome
3.2.3.1.3	Coffin-Lowry syndrome
3.2.3.1.4	Alpha-thalassemia/impaired intellectual development (ATRX) syndrome
3.2.3.2	Intellectual disability syndromes associated with autosomal genes
3.2.3.2.1	Cohen syndrome
3.2.3.2.2	Angelman syndrome
3.3	***Neurological disorders***
3.3.1	Malformations of the brain and spinal cord
3.3.1.1	Microcephaly
3.3.1.2	Macrocephaly
3.3.1.3	Neural tube defects
3.3.1.4	Hydrocephalus (incl. *L1CAM*-associated disorders)
3.3.1.5	Holoprosencephaly and septo-optic dysplasia
3.3.1.6	Neuronal migration disorders (lissencephaly, periventricular nodular heterotopia)
3.3.1.7	Cerebellar morphological anomalies
3.3.2	Movement disorders
3.3.2.1	Cerebellar ataxia (incl. Friedreich ataxia)
3.3.2.2	Hereditary spastic paraplegias
3.3.2.3	Huntington disease and other choreas
3.3.2.4	Dystonias and paroxysmal disorders (including dopa-responsive dystonia)
3.3.2.5	Parkinson disease and atypical parkinsonism
3.3.3	Neurodegenerative disorders and dementias
3.3.3.1	Dementias (Alzheimer, familial, early-onset, frontotemporal)
3.3.3.2	Neurodegeneration with brain iron accumulation (NBIA)
3.3.3.3	Leukodystrophies (Pelizaeus-Merzbacher, X-linked adrenoleukodystrophy)
3.4	***Epilepsies***
3.4.1	Classification of epilepsies by onset and type
3.4.2	Aetiology of epilepsies
3.4.2.1	Structural epilepsies

3.4.2.2	Metabolic epilepsies
3.4.2.3	Channelopathies (incl. *SCN1A-*, *KCNQ2-*, *CACNA1A*-related seizures)
3.4.2.4	Other genetic epilepsies
3.4.3	Specific epilepsy syndromes
3.4.3.1	Epileptic encephalopathies (incl. West syndrome)
3.4.3.2	Dravet syndrome
3.4.3.3	*GLUT1* deficiency
3.4.3.4	*GRIN2A*-related seizures
3.4.3.5	*PCDH19*-related seizures
3.5	***Neuromuscular disorders***
3.5.1	Neuromuscular disorders: overview
3.5.1.1	Causes of fetal akinesia
3.5.2	Muscular dystrophies
3.5.2.1	Myotonic dystrophy types 1 and 2
3.5.2.2	Duchenne/Becker muscular dystrophy
3.5.2.3	Other muscular dystrophies (incl. facioscapulohumeral, limb-girdle)
3.5.3	Other primary muscle disorders
3.5.3.1	Malignant hyperthermia
3.5.4	Disorders of the neuromuscular junction
3.5.4.1	Hereditary myasthenias
3.5.4.2	Escobar syndrome
3.5.5	Hereditary motor and sensory neuropathies
3.5.5.1	*PMP22*-associated HMSN type 1 and HNPP
3.5.6	Motor neurone disorders
3.5.6.1	Spinal muscular atrophy
3.5.6.2	Amyotrophic lateral sclerosis
3.6	***Psychiatric disorders***
3.6.1	Schizophrenia and other psychoses
3.6.2	Bipolar disorders and depression
3.6.3	Autism spectrum disorders
3.6.4	Behavioural disorders
3.6.4.1	Behavioural phenotypes associated with syndromes
3.6.4.2	Addictive behaviour
3.7	***Ophthalmological disorders***
3.7.1	Congenital eye malformations
3.7.1.1	Microphthalmia, anophthalmia
3.7.1.2	Coloboma
3.7.1.3	Anterior chamber anomalies (Axenfeld-Rieger syndrome, Peters anomaly)
3.7.2	Disorders of the anterior chamber
3.7.2.1	Cataracts (congenital, non-congenital)
3.7.2.2	Lens dislocation
3.7.2.3	Glaucoma (primary onset glaucoma)
3.7.3	Retinal disorders
3.7.3.1	Non-syndromic retinopathies (incl. Leber congenital amaurosis, *RPE65*-associated RP)
3.7.3.2	Syndromic retinopathies (Bardet-Biedl syndrome, Usher)
3.7.3.3	Macular degeneration (incl. Stargardt disease), retinoschisis
3.7.3.4	Chorioretinal degeneration

3.7.4	Disorders of the optic nerve
3.7.4.1	Leber hereditary optic neuropathy
3.7.5	Other ophthalmologic disorders and anomalies
3.7.5.1	Oculocutaneous albinism
3.7.5.2	Hereditary disorders of colour vision
3.7.6	Disorders of eyelids and eyelashes
3.7.6.1	Blepharophimosis-ptosis-epicanthus inversus syndrome (BPES)
3.8	***Craniofacial anomalies and ear, nose, throat disorders***
3.8.1	Deafness
3.8.1.1	Congenital deafness (sensorineural and conductive hearing impairment)
3.8.1.2	Connexin 26-associated deafness
3.8.1.3	mtDNA-related deafness
3.8.1.4	Non-syndromic deafness
3.8.1.5	Syndromic deafness
3.8.2	Craniosynostoses
3.8.2.1	FGFR-related craniosynostoses (Apert, Crouzon, Muenke, Pfeiffer)
3.8.2.2	Other craniosynostoses (Saethre-Chotzen syndrome)
3.8.3	Cleft lip/palate
3.8.3.1	Non-syndromic cleft lip/palate
3.8.3.2	Syndromic cleft lip/palate
3.8.3.3	Robin sequence
3.8.4	Other craniofacial anomalies and ENT disorders
3.8.4.1	Cleidocranial dysostosis
3.9	***Dental disorders***
3.9.1	Hypodontia/oligodontia/supernumerary teeth (incl. oligodontia-colorectal cancer syndrome)
3.9.2	Amelogenesis imperfecta
3.9.3	Dentinogenesis imperfecta
3.9.4	Disorders of dental eruption/resorption/loss
3.10	***Disorders of the heart***
3.10.1	Congenital heart malformations
3.10.2	Sudden cardiac death (incl. child vs. adult)
3.10.3	Coronary artery disease (dyslipidaemias: see metabolic)
3.10.4	Hereditary cardiomyopathies (including DD causes such as metabolic, mitochondrial, neuromuscular)
3.10.4.1	Hypertrophic cardiomyopathy (HCM)
3.10.4.2	Dilated cardiomyopathy (DCM)
3.10.4.3	Arrhythmogenic right ventricular cardiomyopathy (ARVC)
3.10.4.4	Left ventricular non-compaction
3.10.4.5	Cardiac amyloidosis (transthyretin amyloidosis, TTR)
3.10.5	Hereditary arrhythmia syndromes
3.10.5.1	Brugada syndrome
3.10.5.2	Long QT syndrome (incl. Jervell and Lange-Nielsen syndrome)
3.10.5.3	Catecholaminergic polymorphic ventricular tachycardia
3.11	***Multisystemic Vascular Disorders***
3.11.1	Vascular malformations

3.11.1.1	Sturge-Weber syndrome, Klippel-Trénaunay-Weber syndrome
3.11.1.2	Other vascular malformations (incl. glomuvenous malformations)
3.11.2	Neurovascular disorders
3.11.2.1	Cerebral cavernous malformations
3.11.2.2	Cerebral aneurysms
3.11.2.3	CADASIL
3.11.3	Hereditary arterial disease
3.11.3.1	Hereditary Thoracic Aortic Diseases
3.11.4	Other vascular disorders
3.11.4.1	Hereditary Haemorrhagic Telangiectasia (Rendu-Osler)
3.11.4.2	Congenital lymphoedema
3.12	***Respiratory disorders***
3.12.1	Congenital thoracic malformations
3.12.1.1	Congenital pulmonary airway malformations (CPAM)
3.12.1.2	Tracheo-oesophageal fistula
3.12.2	Diseases associated with chronic productive cough
3.12.2.1	Cystic fibrosis (CF)
3.12.2.2	Primary ciliary dyskinesia (PCD)
3.12.2.3	Alpha-1 antitrypsin deficiency (AATD)
3.12.3	Interstitial lung diseases
3.12.3.1	Interstitial lung disease including surfactant deficiency
3.12.3.2	Idiopathic pulmonary fibrosis
3.12.4	Other lung diseases
3.12.4.1	Asthma bronchiale
3.12.4.2	Pulmonary hypertension (PH)
3.13	***Hepatological disorders***
3.13.1	Cholestatic diseases and hyperbilirubinaemias
3.13.1.1	Biliary atresia
3.13.1.2	Crigler-Najjar syndrome, Gilbert syndrome
3.13.1.3	Progressive familial intrahepatic cholestasis
3.13.1.4	Bile acid biosynthesis disorders
3.13.2	Hereditary liver diseases
3.13.2.1	Neonatal liver disease
3.13.2.2	Genetic liver disease after the neonatal period
3.14	***Digestive and gastrointestinal disorders***
3.14.1	Gastrointestinal malformations
3.14.1.1	Hirschsprung disease
3.14.1.2	Intestinal malrotation, pyloric stenosis
3.14.2	Genetic malabsorption disorders
3.14.2.1	Lactose intolerance
3.14.2.2	Disaccharide malabsorption
3.14.2.3	Hereditary primary diarrhoeas
3.14.3	Inflammatory gastrointestinal disorders
3.14.3.1	Hereditary pancreatitis
3.14.3.2	Inflammatory bowel diseases
3.15	***Renal and urinary tract disorders***

3.15.1	Congenital anomalies of the kidney and urinary tract (CAKUT)
3.15.1.1	Renal agenesis, Potter sequence
3.15.1.2	Other non-syndromic conditions
3.15.1.3	Syndromic conditions
3.15.2	Tubulointerstitial Nephropathies (Renal ciliopathies)
3.15.2.1	Polycystic kidney disease (autosomal dominant and recessive)
3.15.2.2	Nephronophthisis
3.15.2.3	Ciliopathies with renal and extrarenal manifestations (Senior-Løken syndrome, Bardet-Biedl syndrome, Joubert syndrome, Meckel-Gruber syndrome)
3.15.2.4	Autosomal dominant tubulointerstitial kidney disease (ADTKD)
3.15.2.5	Nephrocalcinosis
3.15.3	Glomerulopathies
3.15.3.1	Alport syndrome
3.15.3.2	Steroid-resistant nephrotic syndrome (SRNS)
3.15.4	Tubulopathies
3.15.4.1	Bartter syndrome and Gitelman syndrome
3.15.4.2	Renal tubular acidosis
3.15.5	Other hereditary disorders of the kidney and urinary tract
3.15.5.1	Hereditary thrombotic microangiopathies
3.16	***Disorders of sex development and reproduction***
3.16.1	Sex-chromosomal anomalies
3.16.1.1	Turner syndrome
3.16.1.2	Klinefelter syndrome
3.16.1.3	Other sex-chromosomal anomalies
3.16.2	Malformations of the internal and external genitalia
3.16.2.1	Hypospadias
3.16.2.2	Persistent Müllerian duct syndrome
3.16.3	Differences of sex development (DSD)
3.16.3.1	Gonadal dysgenesis
3.16.3.2	Adrenogenital syndrome
3.16.3.3	SRY translocation
3.16.3.4	Androgen receptor deficiency
3.16.3.5	Disorders of androgen synthesis
3.16.4	Reproductive disorders
3.16.4.1	Infertility
3.16.4.2	Recurrent miscarriages
3.17	***Skin disorders***
3.17.1	Abnormal pigmentation
3.17.1.1	Nevi
3.17.1.2	Incontinentia pigmenti
3.17.2	Abnormal cornification: Ichthyoses
3.17.2.1	Non-syndromic ichthyoses
3.17.2.1.2	Ichthyosis vulgaris
3.17.2.1.2	X-linked recessive ichthyosis
3.17.2.1.3	Autosomal recessive congenital ichthyosis
3.17.2.2	Syndromic ichthyoses (Sjögren-Larsson syndrome)
3.17.3	Skin blistering: Epidermolysis bullosa
3.17.3.1	Epidermolysis bullosa simplex

3.17.3.2	Junctional epidermolysis bullosa
3.17.3.3	Dystrophic epidermolysis bullosa
3.17.4	Disorders of skin appendages: Ectodermal dysplasias
3.17.4.1	Hypohydrotic ectodermal dysplasia
3.17.4.2	Hydrotic ectodermal dysplasia
3.17.5	Premature ageing
3.17.5.1	Hutchinson-Gilford-progeria, Werner syndrome
3.17.5.2	Rothmund-Thompson syndrome
3.17.6	Multifactorial genodermatoses
3.17.6.1	Psoriasis vulgaris
3.18	***Connective tissue and musculoskeletal disorders***
3.18.1	Hypermobility
3.18.1	Ehlers-Danlos syndromes
3.18.1	Other collagen disorders
3.18.1	Marfan syndrome
3.18.1	TGF-beta signalling disorders (incl. Loeys-Dietz syndrome)
3.19	***Skeletal disorders***
3.19.1	Skeletal malformations and related anomalies
3.19.1.1	Common skeletal deformities
3.19.1.2	Hand/foot/limb malformations (incl. split hand/foot, polydactyly, limb reduction defects)
3.19.1.3	Arthrogryposis
3.19.1.4	Sequences (Poland, Klippel-Feil)
3.19.2	Bone density disorders
3.19.2.1	Osteogenesis imperfect, decreased bone density
3.19.2.2	Osteopetrosis, increased bone density
3.19.3	Osteochondrodysplasias
3.19.3.1	Clinical approach to osteochondrodysplasias
3.19.3.2	Achondroplasia and other *FGFR3*-related disorders (incl. hypochondroplasia)
3.19.3.3	Campomelic dysplasia and other bent bone dysplasias
3.19.3.4	Chondrodysplasia punctate (XL, brachyphalangic, Conradi-Hünermann syndrome)
3.19.3.5	Stickler syndrome and other collagen II and XI disorders
3.19.3.6	*SHOX*-related disorders (dyschondrosteosis)
3.19.3.7	Frontometaphyseal dysplasia and other filamin-related disorders
3.19.3.8	Multiple synostoses syndrome (Tarsal-Carpal Coalition, and Isolated Stapes Ankylosis)
3.20	***Endocrine disorders***
3.20.1	Adrenal disorders
3.20.1.1	Congenital adrenal hyperplasia
3.20.1.2	ACTH resistance
3.20.2	Disorders of calcium and phosphate homeostasis
3.20.2.1	Primary hyperparathyroidism
3.20.2.2	Familial hypocalciuric hypercalcaemia
3.20.2.3	Pseudohypoparathyroidism and related disorders (Albright hereditary osteodystrophy, McCune-Albright syndrome)
3.20.3	Disorders of glucose and insulin homeostasis
3.20.3.1	Monogenic diabetes mellitus
3.20.3.2	Wolfram syndrome (DIDMOAD)
3.20.3.3	Hyperinsulinism

3.20.4	Growth and genetic obesity syndromes
3.20.4.1	Monogenic obesity syndromes (leptin deficiency)
3.20.5	Hypothalamic and pituitary disorders
3.20.5.1	Hypopituitarism
3.20.5.2	Kallman syndrome
3.20.6	Thyroid disorders
3.20.6.1	Primary congenital hypothyroidism
3.21	***Metabolic/biochemical genetic disorders***
3.21.1	Disorders of amino acid and peptide metabolism
3.21.1.1	Aminoacidopathies and organic acidurias
3.21.1.1.1	Phenylketonuria
3.21.1.1.2	Tyrosinaemia
3.21.1.1.3	Maple syrup urine disease
3.21.1.1.4	Propionic and methylmalonic aciduria
3.21.1.1.5	Homocystinuria
3.21.1.2	Urea cycle disorders
3.21.1.2.1	Ornithine transcarbamylase deficiency
3.21.2	Disorders of carbohydrate metabolism
3.21.2.1	Galactosaemia
3.21.2.2	Glycogen storage disorders
3.21.3	Disorders of fatty acid, carnitine and ketone body metabolism
3.21.3.1	Long-chain fatty acid oxidation deficiency
3.21.3.2	Medium-chain fatty acid oxidation deficiency
3.21.4	Disorders of energy metabolism, mitochondriopathies
3.21.4.1	Clinical approach to mitochondrial disorders
3.21.4.2	Pyruvate dehydrogenase deficiency
3.21.4.3	Creatine deficiency disorders
3.21.4.4	mtDNA-related disorders (incl. MELAS syndrome)
3.21.4.5	mtDNA depletion syndromes
3.21.4.6	Other nuclear mitochondrial disorders
3.21.5	Disorders of lipid metabolism
3.21.5.1	Peroxisomal disorders
3.21.5.1.1	Zellweger spectrum disorders
3.21.5.2	Disorders of sterol synthesis
3.21.5.2.1	Smith-Lemli-Opitz syndrome
3.21.5.3	Disorders of lipoprotein metabolism
3.21.5.3.1	Familial hypercholesterolaemia
3.21.5.3.2	Hypertriglyceridaemias
3.21.5.3.3	Other disorders of lipoprotein metabolism
3.21.6	Disorders of purine, pyrimidine and nucleotide metabolism
3.21.6.1	Myoadenylate deaminase deficiency
3.21.6.2	Lesch-Nyhan syndrome
3.21.7	Porphyrias
3.21.7.1	Acute intermittent porphyria
3.21.7.2	Porphyrias with erosive photodermatosis
3.21.7.3	Porphyrias with acute painful photosensitivity
3.21.8	Congenital disorders of glycosylation (CDG)
3.21.8.1	Phosphomannomutase deficiency

3.21.9	Disorders of complex molecule degradation, lysosomal diseases
3.21.9.1	Sphingolipidoses
3.21.9.1.1	Gaucher disease
3.21.9.1.2	Fabry disease
3.21.9.1.3	Other sphingolipidoses (incl. Krabbe, Niemann-Pick, metachromatic leukodystrophy
3.21.9.2	Mucopolysaccharidoses
3.21.9.2.1	Hurler/Scheie disease
3.21.9.2.2	Pompe disease
3.21.9.2.3	Sanfilippo disease
3.21.9.2.4	Morquio disease
3.21.9.3	Other lysosomal diseases
3.21.9.3.1	Neuronal ceroid lipofuscinoses
3.21.10	Disorders of vitamin and cofactor metabolism
3.21.10.1	Disorders of folate metabolism (incl. MTHFR)
3.21.10.2	Disorders of vitamin B6 metabolism (incl. pyridoxine-responsive seizures)
3.21.10.3	Disorders of vitamin B12 metabolism
3.21.11	Disorders of the metabolism of trace elements and minerals
3.21.11.1	Menkes disease
3.21.11.2	Wilson disease
3.21.11.3	Haemochromatosis
3.22	***Immunodeficiency, autoinflammatory/autoimmune disorders***
3.22.1	Primary immunodeficiencies
3.22.1.1	Severe combined immunodeficiencies
3.22.1.2	Congenital neutropaenias (cyclic or severe congenital neutropaenia, Shwachman-Diamond syndrome)
3.22.1.3	Agammaglobulinaemia (Bruton disease)
3.22.1.4	Chronic granulomatous disease
3.22.2	Autoinflammatory disorders
3.22.2.1	Familial Mediterranean fever
3.22.2.2	Other inflammasome-related disorders (CAPS, CINCA, Muckle-Wells syndrome)
3.22.2.3	Non inflammasome-related disorders (incl. TRAPS, Blau)
3.22.2.4	Interferonopathies
3.22.3	Other conditions
3.22.3.1	Hereditary angioedema
3.22.3.2	Autoimmune diseases
3.22.3.3	Paediatric rheumatic disease
3.23	***Haematological and coagulation disorders***
3.23.1	Haemoglobinopathies
3.23.1.1	Alpha-thalassaemia
3.23.1.2	Beta-thalassaemia and sickle cell disease
3.23.2	Other hereditary anaemias
3.23.2.1	Erythrocyte membrane defects (incl. spherocytosis)
3.23.2.2	Haemolytic anaemia due to an enzyme deficiency
3.23.3	Hereditary bone marrow failure
3.23.3.1	Blackfan-Diamond syndrome
3.23.4	Hereditary coagulation disorders
3.23.4.1	Haemophilia
3.23.4.2	Thrombophilia (incl. prothrombin, factor V Leiden)

3.23.4.3	Von Willebrand disease
3.23.4.4	Platelet disorders (incl. Glanzmann thrombasthenia, Bernard-Soulier syndrome)
3.23.5	Blood groups
3.23.5.1	ABO blood group
3.23.5.1	Other blood groups (incl. Rhesus factor)
3.24	***Tumours and tumour predisposition syndromes***
3.24.1	Leukaemias and lymphomas
3.24.2	Solid tumours in childhood
3.24.2.1	Retinoblastoma
3.24.2.2	Neuroblastoma
3.24.2.3	Wilms tumour
3.24.3	Neurocutaneous syndromes
3.24.3.1	Neurofibromatosis type 1
3.24.3.2	Neurofibromatosis type 2
3.24.3.3	Tuberous sclerosis
3.24.3.4	Von-Hippel-Lindau syndrome
3.24.3.5	Gorlin (Goltz) syndrome (basal cell nevus syndrome)
3.24.3.6	*PTEN* Hamartoma Tumour syndrome (incl. Cowden syndrome)
3.24.4	Breast and ovarian cancer
3.24.4.1	Breast Cancer
3.24.4.2	Ovarian cancer
3.24.5	Colon cancer and other gastrointestinal cancers
3.24.5.1	Lynch syndrome (non-polyposis colorectal cancer)
3.24.5.2	Gastrointestinal polyposis syndromes (incl. FAP, *MUTYH*-associated, juvenile polyposis)
3.24.5.3	Peutz-Jeghers syndrome
3.24.5.4	Diffuse Gastric Cancer (HDGC)
3.24.4	Thyroid cancer and other endocrine cancers
3.24.4.1	Multiple endocrine neoplasia (MEN) I, II
3.24.4.2	Familial pituitary cancers
3.24.4.3	Paraganglioma-pheochromocytoma syndrome
3.24.4	Other tumour predisposition syndromes
3.24.4.1	Li-Fraumeni syndrome
3.24.4.2	Malignant melanoma
3.24.4.3	Renal cancer (incl. hereditary papillary carcinoma)
3.24.4.4	Birt-Hogg-Dubé syndrome
3.24.5	Constitutional DNA repair deficiencies
3.24.5.1	DNA mismatch repair deficiencies
3.24.5.1.1	Constitutional mismatch repair deficiency syndrome (CMMRD)
3.24.5.2	Base excision repair deficiencies
3.24.5.3	Nucleotide excision repair deficiencies
3.24.5.3.1	Xeroderma pigmentosum
3.24.5.3.2	Cockayne syndrome
3.24.5.3.3	Trichothiodystrophy
3.24.5.4	Chromosome instability syndromes
3.24.5.4.1	Ataxia telangiectasia
3.24.5.4.2	Fanconi anaemia
3.24.5.4.3	Bloom syndrome
3.24.5.4.4	Nijmegen breakage syndrome