E06/S/a

2013/14 NHS STANDARD CONTRACT
FOR METABOLIC DISORDERS (ADULT)

PARTICULARS, SCHEDULE 2 – THE SERVICES A. SERVICE SPECIFICATIONS

Service Specification No.	E06/S/a
Service	Metabolic Disorders (Adult)
Commissioner Lead	
Provider Lead	
Period	12 months
Date of Review	

1. Population Needs

1.1 National/local context and evidence base

National Context

Inherited Metabolic Disorders (IMDs) cover a group of over 600 individual conditions, each caused by defective activity in a single enzyme or transport protein. Although individually metabolic conditions are rare, the incidence being less than 1.5 per 10,000 births, collectively they are a considerable cause of morbidity and mortality. The diverse range of conditions varies widely in presentation and management according to which body systems are affected. For some patients presentation may be in the newborn period, whereas for others with the same disease (but a different genetic mutation) onset may be later, including adulthood.

Without early identification and/or introduction of specialist diet or drug treatments, patients face severe disruption of metabolic processes in the body such as energy production, manufacture of breakdown of proteins, and management and storage of fats and fatty acids. The result is that patients have either a deficiency of products essential to health or an accumulation of unwanted or toxic products. Without treatment many conditions can lead to severe learning or physical disability and death at an early age.

The rarity and complex nature of IMD requires an integrated specialised clinical and laboratory service to provide satisfactory diagnosis and management. This is in keeping with the recommendation of the Department of Health's UK Plan for Rare Disorders consultation to use specialist centres.

Approximately 10-12,000 paediatric and adult patients attend UK specialist IMD centres, but a significant number of patients remain undiagnosed or are 'lost to

follow-up'. These patients would benefit from early investigation and regular specialist monitoring to minimise major organ crises in later life.

Approximately 1,000 new paediatric and adult IMD patients are identified each year.

IMD clinical disease is lifelong, usually progressive and may affect one or more organ systems. Management requires a co-ordinated approach from the core IMD multidisciplinary team, comprising IMD medical, dietetic, nursing staff, with access to IMD laboratory expertise as well as support from many different medical specialties and professions allied to medicine. Undiagnosed or 'lost to follow-up' patients may present to almost any medical specialty and may be subject to several inconclusive investigations for individual symptoms. Increased professional education, together with expertise concentrated in a limited number of centres, allows for the earlier recognition, diagnosis and treatment of the underlying IMD condition and its potential complications, leading to reduced disease burden.

Current and proposed newborn bloodspot screening programmes identify some IMD conditions; in these circumstances, other family members may require advice or medical investigation. New technologies for diagnosis and more effective treatments promote improved survival rates and quality of life.

The IMD specialty covers the following service specifications:

- Specialised Services for Inherited Metabolic Disorders (paediatrics)
- Specialised Services for Inherited Metabolic Disorders (adults)
- Specialised Services for Inherited Metabolic Disorders (laboratory services)

Approved IMD centres will be the primary providers for the IMD service. Individual centres that are unable to fulfill all components of the service specification (for example, the 24-hour telephone advisory service commitment) will form clinical networks with adjacent approved centres

Evidence Base

A major needs assessment, Metabolic Pathways, Networks of Care (Hilary Burton, Public Health Genetics, 2005) (www.phgfoundation.org), concluded that there is wide variation of service provision across the UK, few dedicated IMD consultants, specialist IMD dietitians and specialist nursing staff, and poor outreach clinic provision.

The Department of Health consultation in May 2012 in response to the Genetic Alliance's UK Rare Disease Strategy (www.raredisease.org.uk) highlights the problems of commissioning services where there are low patient volumes, and proposes 'hub and spoke' networks of clinical and laboratory units, and active participation in patient registers for service planning and research purposes.

The specialty's professional bodies for clinical and laboratory services, including British Inherited Metabolic Disease Group (www.bimdg.org.uk) and MetBioNet (www.metbio.net) provide key clinical guidelines.

NICE guidance on Familial Hypercholesterolaemia (FH) recommended that paediatric patients are referred to specialised IMD centres (www.nice.org.uk)

Specialised Metabolic Disorders Services (all ages), Specialised Services National Definitions Set No 36 (3rd ed), 2009 (www.bimdg.org.uk)

Rare Disease Centres Proposal, Advisory Group for National Specialised Services (www.bimdg.org.uk)

Our Inheritance, Our Future: Realising the potential of genetics in the NHS, Department of Health 2003 (www.dh.gov.uk)

2. Scope

2.1 Aims and objectives of service

Aims of Specialised IMD centres

The service aims to identify and diagnose patients who are suspected of having an IMD, to improve life expectancy and quality of life for adults affected by one of the IMDs detailed in Appendix 1 (list of IMD conditions for proposed ICD11 (a global health information standard) codes).

Objectives of specialised IMD centres

The adult IMD Centre will:

- provide 24/7 access to clinical advice in conjunction with other adult and paediatric centres in an agreed service provider network
- provide high-quality clinical expertise in accordance with national policy and guidance where available or in agreement with accepted clinical practice to:
    - provide timely diagnosis with appropriate counselling and psychological support to the patient and family/carers
    - provide dedicated IMD inpatient and outpatient facilities
    - provide high quality proactive diet and/or drug treatment and care
    - agree and monitor compliance of care pathways and treatment protocols (elective and emergency)
    - ensure smooth transition from paediatric to adult care
    - ensure equity of access to services for the IMD population
- provide in-house training and education for IMD physicians completing Royal College of Physicians and Royal College of Pathology metabolic training programme
- provide expert advice and education to primary, secondary[1] and tertiary care provider units under agreed shared care arrangements where clinically appropriate, and to professionals of other specialised services, e.g. nephrology, cardiology, neurology, linked to IMD conditions

[1] inc Orthopaedics, gastroenterology, urology, gynaecology, etc

- provide expert advice to non-medical professionals, including local authorities and the voluntary sector, to facilitate holistic care for IMD patients and support to their families/carers.

2.2 Service description/care pathway

Overview

IMDs are inherited lifelong conditions and patients will access routine care and ongoing specialised care provided by appropriately trained specialist clinical staff throughout their lifetime. The IMD centre will provide care related to the patient's IMD condition. The configuration of care provision will be based on local prevalence, expertise and availability of designated IMD service providers. The IMD centres will liaise with other NHS Trusts to provide appropriate and sustainable outreach clinics All adult and paediatric IMD centres will establish formal links and referral pathways, and will work co-operatively to ensure 24/7 telephone advice service within agreed network configurations. The centre will agree with the nominated Area Team (AT) of NHS England to:

- take lead clinical responsibility for managing the care of referred IMD patients. register all consented patients on an IMD Centre patient database in preparation for a proposed National IMD Register, and to ensure that individual records are complete and up-to-date
- provide appropriate clinical care in outreach facilities
- generate and publish evidence of effective treatments
- support the production of a national training and development plan for all healthcare staff involved in the delivery of IMD services
- participate in and contribute to national and international research programmes, in collaboration with the IMD Clinical Reference Group (CRG), to enhance professional understanding of individual syndromes.

Patient Pathway

Patients with IMDs will require access to expert care and advice throughout their lives. The patient's condition will require regular monitoring, supported by laboratory and other diagnostic tests. In some circumstances, there may be opportunities for shared care arrangements with primary and/or secondary care providers, but all patients will require regular follow-up attendances and support from the centre or outreach clinic

Referral

The adult IMD centre will:

- Accept referrals from:
  - another NHS IMD consultant
  - IMD paediatric centres as part of the patient transition programme
  - the patient's GP, and secondary and tertiary care consultants (where it is agreed with the IMD Centre that the patient's symptoms suggest an underlying metabolic disorder)

    - designated IMD laboratories
- operate a single referral list
- provide a 24/7 telephone advice service under an agreed provider network for referral or for patients with acute severe illness that may be caused by an IMD
- provide inpatient facilities to stabilise and monitor clinically appropriate patients
- carry out a core IMD MDT assessment of all referred patients within three months for non-urgent referrals
- provide access to and co-ordinate results and assessment from a range of diagnostic tests and from expertise in other specialties where appropriate

Initial Care

The adult IMD centre will:

- offer all patients with a confirmed diagnosis of IMD a complete assessment, as per published U.K. guidelines where available or as clinically indicated for IMD syndromes for which guidelines do not exist.
- establish a baseline against which disease progression and response to treatment can be measured
- agree the need for any therapeutic intervention, either specific or supportive
- offer treatment to all patients who might potentially benefit; eligibility for treatment to be determined as set out in relevant guidelines or as clinically indicated
- provide immediate care for patients with acute severe illness resulting from an IMD. Commence therapy for eligible patients within 12 weeks of:
    - initial referral for those already diagnosed or
    - from receipt of a firm diagnosis for those referred to the designated centres for further testing
- provide age-appropriate written and/or electronic material, including provision of information in the patient/family's first language, relating to the IMD condition to patients and their families/carers

Ongoing care

The adult IMD centre will provide:

- a minimum annual core IMD MDT review of all patients
- regular patient reviews as per national guidelines or clinical practice with written and electronic records of current treatment and patient response
- access to inpatient and critical care facilities where appropriate
- access to other specialised services, e.g. hepatology, cardiology, etc., as appropriate
- appropriate pharmaceutical and dietary therapy
- regular laboratory and other diagnostic tests as appropriate to monitor patient response to diet and/or medication
- patient-centred services, sensitive to the individual's physical, psychological and emotional needs and supported through the provision of patient-appropriate information (as above)
- access to appropriate shared care arrangements with primary and/or

secondary care providers
- options for home therapy where appropriate, supported by regular clinical monitoring
- clinical nurse specialist telephone advice service for patients and their families/carers, healthcare professionals and non-healthcare and voluntary sector professionals

Outreach Clinics

Clinicians and commissioners will work together to identify patient cohorts with poorer geographic access to IMD Centres, and to promote appropriate outreach facilities and local support structures.

Transition from paediatric to adult IMD services

Paediatric and adult IMD centres will develop close working relationships within local networks. The centres will work together to ensure smooth and effective transition of patients to appropriate facilities according to best practice guidelines.

The adult IMD centre will:
- accept referrals by IMD Consultant Paediatricians of appropriate adolescents
- provide an agreed period of joint paediatric/adult clinics to ensure seamless transfer of adolescent IMD patients to adult services
- agree and provide formalised operational transition policy in each unit
- provide age-appropriate written and/or electronic information to patients and their families/carers (as above)

Palliative or end-of-life care

The adult IMD centre will:
- provide symptom control where appropriate for patients with untreatable or degenerative conditions
- liaise actively with NHS and non-NHS professionals to ensure access to appropriate palliative or end-of-life services
- monitor patient response on a regular basis
- generate and publish evidence of effective palliative or end-of-life care for adult patients with IMDs.

Infrastructure requirements

Approved centres are the primary providers for IMD services. Individual centres that are unable to fulfill all components of the service specification, for example the 24-hour on-call commitment) will form formal clinical networks with other adjacent approved centres. IMD centres will provide outreach clinics where appropriate.

Each adult IMD centre will be staffed by a core team from a range of suitably qualified health professionals including the following people:
- A named service/business manager

- At least 2 wte specialised IMD physicians
- At least 1 wte Senior Specialist IMD dietitian (**) supported by a dietetic team capable of delivering the service
- At least 1 wte Specialist IMD nurse supported by a nursing team capable of delivering the service
- Therapists, including physiotherapist, occupational therapist and psychotherapist
- A named pharmacist
- A unit secretary responsible for triaging telephone enquiries and correspondence
- Appropriate administrative and clerical support for the proper management of the service

(**) Specialist IMD dietitian – minimum qualifications of MSc qualification in nutrition and dietetics, or equivalent specialist experience; will be registered with the statutory regulatory body, the Health Professions Council (HPC) and the professional body, the British Dietetic Association (BDA. The minimum dietetic caseload is 100 patients per annum, dependent upon casemix

The centre will have formal arrangements with one or more designated IMD laboratory (see separate IMD Laboratory Services specification) for the biochemical diagnosis and monitoring of IMD patients. Such arrangements will include regular meetings with the laboratory IMD Consultant Clinical Scientist and other appropriate laboratory staff to discuss the interpretation of results.

The IMD centre will have access to expert opinion and support from other specialised clinical services, e.g. intensive care, cardiology, nephrology, neurology, etc., and will provide access to all services including social work support, commonly found in a regional acute hospital.

Patient registers/database

Accurate coding and classification of rare disorders is necessary for determining correct management, providing information on outcome and directing research. The value of such registers to patients is discussed in the chapter ‘Empowering those affected by rare conditions’ in the Department of Health’s 2012 document ‘Consultation on the United Kingdom Plan for Rare Diseases’.

The IMD centre will ensure that all patients are invited to have their information collected and entered onto a national IMD register.

All IMD centres and laboratories will co-operate in developing a national register of research trials and outcomes.

Annual reports

The IMD centre will produce annual audit and governance reports – see Section 4.

Pregnancy

Pregnant women with pre-existing conditions as discussed in this specification require assessment and/or management from highly specialist tertiary maternity care delivered within a dedicated multidisciplinary service staffed by a maternal medicine specialist, a physician, and supporting multidisciplinary team with extensive experience of managing the condition in pregnancy.

In view of this, nationally commissioned condition specific services must have outreach arrangements with highly specialized tertiary maternity units with access to appropriate tertiary medical, surgical, fetal medicine, clinical genetics and level 3 Neonatal Intensive Care services. These specialized maternity services must have a critical mass of activity to maintain expertise, ensure best practice, training opportunities and for the organizational infrastructure, staffing, facilities and equipment to be clinically and economically efficient. They should have robust risk management and performance monitoring processes.

All such women must receive personalized pre-pregnancy and maternity care planning from specialised tertiary maternity services to allow optimal disease management in the context of the pregnancy. This will reduce avoidable morbidity, mortality and unnecessary intervention for mother and baby.

Women with conditions discussed in this specification must be referred immediately once they are pregnant to plan their care. This must include access to termination of pregnancy and specialist advice re contraception. The individualised care plan must cover the ante natal, intrapartum and postnatal periods. It must include clear instructions for shared care with secondary services, when appropriate including escalation and transfer protocols and clear guidelines for planned and emergency delivery.

2.3 Population covered

The service outlined in this specification is for patients ordinarily resident in England(*); or otherwise the commissioning responsibility of the NHS in England (as defined in Who Pays?: Establishing the responsible commissioner and other Department of Health guidance relating to patients entitled to NHS care or exempt from charges).

(*) Note: For the purposes of commissioning health services, this EXCLUDES patients who, whilst resident in England, are registered with a GP practice in Wales, but INCLUDES patients resident in Wales who are registered with a GP practice in England.

Specifically, the service is commissioned for all diagnosed IMD patients and patients referred with a suspected IMD condition listed in Appendix 1, irrespective of gender, age, sex, disability or religious belief.

2.4 Any acceptance and exclusion criteria

Acceptance criteria

The adult IMD centre will accept referral of a patient with an IMD diagnosis or a patient with a suspected IMD condition as listed in Appendix 1 by the following professionals:

- Another NHS IMD consultant
- The patient's GP, and secondary and tertiary care consultants where it is agreed that the patient's symptoms suggest an underlying metabolic disorder
- Designated IMD laboratories

Exclusions

The specification excludes:

- Treatment of adult patients with Heterozygous Familial Hypercholesterolaemia (Heterozygous FH); these patients should be referred to local district general hospital Lipid Clinics
- Adult critical care
- Surgical procedures and interventions including:
    - Haemopoetic Stem Cell Transplants (HSCT)
    - Bone Marrow Transplantation (BMT)
    - Organ transplants, e.g. liver, kidney
    - Spinal surgery/botox
    - Renal dialysis
- Pre-implantation genetic diagnosis
- Investigational drugs and procedures that are part of a research protocol

2.5 Interdependencies with other services

Co-located services

Appropriate critical care facilities

Interdependent services

Specialised IMD laboratory services, and other diagnostic tests.

Many IMD patients have co-morbid medical syndromes, including cardiac, renal and neurological conditions. It is therefore essential that centres establish and maintain strong clinical links with other specialised services as follows:

- Specialised Blood and Marrow Transplantation Services (all ages)
- Specialised Services for Women's Health (adult)
- Assessment and Provision of Equipment for People with Complex Physical Disabilities (all ages)

- Specialised Spinal Services (all ages)
- Specialised Rehabilitation Services for Brain Injury and Complex Disability (adult)
- Specialised Neurosciences Services (adult)
- Specialised Renal Services (adult)
- Specialised Cardiology and Cardiac Surgery Services (adult)
- Specialised Services for Liver, Biliary and Pancreatic Medicine and Surgery (adult)
- Medical Genetics Services (all ages)
- Specialised Mental Health Services (all ages)
- Specialised Rheumatology Services (all ages)
- Specialised Endocrinology Services (adult)
- Specialised Respiratory Services (adult)
- Specialised Orthopaedic Services (adult)
- Specialised Ophthalmology Services (adult)

Related services

IMD conditions are life-long, and centres will need to establish links with primary and secondary care units, particularly where there are shared care arrangements, as well as non-NHS professionals such as social services, education and patient groups.

3. Applicable Service Standards

3.1 Applicable national standards e.g. NICE, Royal College

The key service policy and legislative documents which support the provision of high quality IMD services are listed below. This specification is not intended to duplicate, replicate or supersede these policies and guidelines but to build upon them.

Core Standards	NICE CG071 Familial Hypercholesterolaemia, NICE August 2008 (www.nice.org.uk)
Recommended Standards	Rare Disease Centres Proposal, Advisory Group for National Specialised Services (AGNSS), 2011 (www.bimdg.org.uk) Metabolic Pathways, Networks of Care, Hilary Burton, Public Health Genetics Unit (PGHU), 2005 (www.phgfoundation.org) NHS Specialised Services Definition No.36: Specialised Metabolic Disorders (all ages) 3rd edition, 2010 (www.bimdg.org.uk)

4. Key Service Outcomes

The aim of the IMD service is to identify and diagnose patients who are suspected of having an IMD, and to reduce levels of morbidity and mortality of diagnosed patients. The centres will work with the CRG Quality lead to develop key service outcomes through national quality dashboards and CQUINs. Baseline and comparative data will be dependent upon information provided by each centre prior to the introduction of national initiatives including:

- National patient register
- National register of research trials and outcomes
- Annual audit / governance report

Process measures from designated centres will be used as a proxy for outcomes of:

- Early diagnosis
- Improved patient life expectancy
- Prevention of avoidable death from IMD or its complications
- Improved quality of life (patient/family questionnaires)
- Fewer investigations in other specialties, e.g. cardiology, nephrology, etc.

Appendix 1 - List of IMD Conditions for proposed ICD11 codes

Disease group / disease	ICD10	OMIM
1. Disorders of amino acid and peptide metabolism		
1.1. Urea cycle disorders and inherited hyperammonaemias		
1.1.1. Carbamoylphosphate synthetase I deficiency		237300
1.1.2. N-Acetylglutamate synthetase deficiency		237310
1.1.3. Ornithine transcarbamylase deficiency		311250
1.1.4. Citrullinaemia type1		215700
1.1.5. Argininosuccinic aciduria		207900
1.1.6. Argininaemia		207800
1.1.7. HHH syndrome		238970
1.1.8. Citrullinemia Type 2		603859
1.1.9. Hyperinsulinemic hypoglycemia and hyperammonemia caused by activating mutations in the GLUD1 gene		138130
1.1.10. Other disorders of the urea cycle		238970
1.1.11. Unspecified hyperammonaemia		238970
1.2. Organic acidurias		
1.2.1. Glutaric aciduria		
1.2.1.1. Glutaric aciduria type I		231670
1.2.1.2. Glutaric aciduria type III		231690
1.2.2. Propionic aciduria	E711	232000
1.2.3. Methylmalonic aciduria	E711	251000
1.2.3.1. Methylmalonyl-CoA mutase deficiency		
1.2.3.2. Methylmalonyl-CoA epimerase deficiency		251120
1.2.3.3. Methylmalonic aciduria, unspecified		
1.2.4. Isovaleric aciduria	E711	243500
1.2.5. Methylcrotonylglycinuria	E744	210200
1.2.6. Methylglutaconic aciduria	E712	250950
1.2.6.1. Methylglutaconic aciduria type I	E712	250950
1.2.6.2. Methylglutaconic aciduria type II	E723	302060
1.2.6.3. Methylglutaconic aciduria type III	E723	258501
1.2.6.4. Methylglutaconic aciduria type IV	E723	250951
1.2.6.5. Methylglutaconic aciduria type V		610198
1.2.7. 3-Hydroxy-3-methylglutaric aciduria	E728	246450
1.2.8. 2-Methylbutyric aciduria		610006
1.2.9. 2-Methyl-3-hydroxybutyric aciduria		300438
1.2.10. Alpha-methylacetoacetic aciduria	E712	203750
1.2.11. Isobutyric aciduria		611283
1.2.12. Methacrylic aciduria	E711	250620
1.2.13. 3-Hydroxyisobutyric aciduria		236795
1.2.14. Methylmalonate semialdehyde dehydrogenase deficiency		603178

Disease group / disease	ICD10	OMIM
1.2.15. L-2-hydroxyglutaric aciduria		236792
1.2.16. D-2-hydroxyglutaric aciduria		600721
1.2.16.1. D-2-hydroxyglutarate dehydrogenase deficiency		609186
1.2.16.2. Mitochondrial isocitrate dehydrogenase deficiency		147650
1.2.17. Aminoacylase deficiency		
1.2.17.1. Aminoacylase 1 deficiency		609924
1.2.17.2. Aminoacylase 2 deficiency		271900
1.2.18. Methylmalonate semialdehyde dehydrogenase deficiency		603178
1.2.19. Other organic acidurias		
1.3. Disorders of the metabolism of branched-chain amino acids not classified as organic acidurias		
1.3.1. Branched-chain amino acid transferase		238340
1.3.2. Maple syrup urine disease	E710	248600
1.3.2.1. BCKD E1 alpha subunit of deficiency		
1.3.2.2. BCKD E1 beta subunit of deficiency		
1.3.2.3. Dihydrolipoamide branched chain transacylase deficiency		248610
1.3.2.4. Unspecified BCKD deficiency		248610
1.3.3. Other disorders of branched-chain amino acid metabolism		
1.4. Disorders of phenylalanine or tyrosine metabolism		
1.4.1. Phenylalanine hydroxylase deficiency		261600
1.4.2. Tyrosinaemia type II		276600
1.4.3. Tyrosinaemia type III		276710
1.4.4. Hawkinsinuria		140350
1.4.5. Alkaptonuria		203500
1.4.6. Tyrosinaemia type I		276700
1.4.7. Transient tyrosinaemia of the neonate		
1.4.8. Other disorders of phenylalanine or tyrosine metabolism		
1.5. Disorders of the metabolism of sulphur amino acids		
1.5.1. Methionine adenosyltransferase I/III deficiency	E721	250850
1.5.2. Glycine N-methyltransferase deficiency	E728	606664
1.5.3. S-adenosylhomocysteine hydrolase deficiency	E721	180960
1.5.4. Cystathionine beta-synthase deficiency	E721	263200
1.5.5. Cystathionase deficiency	E721	219500
1.5.6. Isolated sulfite oxidase deficiency	E721	272300
1.5.7. Methionine synthase deficiency-cblG	E721	250940
1.5.8. Methionine synthase reductase deficiency-cblE	E721	236270
1.5.9. Other genetic defect in methionine cycle or sulfur amino acid metabolism	E721	
1.5.10. Unspecified disorder of homocysteine metabolism	E721	

Disease group / disease	ICD10	OMIM
1.5.11. Unspecified disorder of methionine metabolism	E721	
1.5.12. Secondary non-genetic disorders of methionine cycle and other sulfur amino acids	E729	
1.6. Disorders of histidine, tryptophan or lysine metabolism		
1.6.1. Histidinaemia	E708	235800
1.6.2. Urocanase deficiency	E708	276880
1.6.3. Glutamate formiminotransferase deficiency	E728	229100
1.6.4. Tryptophanaemia	E708	
1.6.5. Hyperlysinaemia		
1.6.5.1. Hyperlysinaemia type I		238700
1.6.5.2. Hyperlysinaemia type II		268700
1.6.6. 2-Aminoadipic aciduria		204750
1.6.7. 2-Oxoadipic aciduria		245130
1.6.8. Hydroxykynureninuria		236800
1.6.9. Hydroxylysinuria		236900
1.7. Disorders of serine, glycine or glycerate metabolism		
1.7.1. Phosphoglycerate dehydrogenase deficiency	E728	606879
1.7.2. Phosphoserine phosphatase deficiency		172480
1.7.3. Phosphoserine aminotransferase deficiency		610992
1.7.4. Nonketotic hyperglycinaemia	E725	238300
1.7.4.1. P protein deficiency, GLDC gene		238300
1.7.4.2. T protein deficiency, AMT gene		238310
1.7.4.3. H protein deficiency, GCSH gene		238330
1.7.5. Sarcosinaemia	E725	268900
1.7.6. D-glyceric aciduria		220120
1.8. Disorders of ornithine or proline metabolism		
1.8.1. Ornithine aminotransferase deficiency		
1.8.2. Hyperprolinaemia type I		
1.8.3. Hyperprolinaemia type II		
1.8.4. Hypoprolinaemia		
1.8.5. Cutis laxa, autosomal recessive, type IIb		179035
1.9. Disorders of amino acid transport		
1.9.1. Lysinuric protein intolerance	E723	222700
1.9.2. Cystinuria	E720	220100
1.9.3. Cystinuria-hypotonia syndrome (contiguous gene defect)		606407
1.9.4. Hartnup disease	E720	234500
1.9.5. Iminoglycinuria		242600
1.9.6. Lowe syndrome	E720	309000
1.9.7. Other disorders of amino acid transport		
1.10. Other disorders of amino acid metabolism		
1.10.1. Glutamine synthetase deficiency		

Disease group / disease	ICD10	OMIM
1.11. Disorders of the gamma-glutamyl cycle		
1.11.1. Glutathionuria		
1.11.2. Cysteinylglycinase deficiency		
1.11.3. Oxoprolinuria		260005
1.11.4. Gamma-glutamylcysteine synthetase deficiency		230450
1.11.5. Glutathione synthetase deficiency		266130
1.12. Other disorders of peptide metabolism		
1.12.1. Prolidase deficiency		170100
1.12.2. Carnosinaemia		212200
1.12.3. Homocarnosinosis	E728	236130
1.13. Other disorders of amino acid and protein metabolism		
2. Disorders of carbohydrate metabolism		
2.1. Disorders of galactose metabolism		
2.1.1. Classical galactosaemia		230400
2.1.2. Galactokinase deficiency		230200
2.1.3. Uridine diphosphate galactose-4-epimerase deficiency		230350
2.2. Disorders of fructose metabolism		
2.2.1. Essential fructosuria		229800
2.2.2. Hereditary fructose intolerance		229600
2.3. Disorders of pentose metabolism		
2.3.1. Essential pentosuria		260800
2.3.2. Ribose-5-phosphate isomerase deficiency		608611
2.3.3. Transaldolase deficiency		606003
2.4. Disorders of glycerol metabolism		
2.4.1. Glycerol kinase deficiency		307030
2.4.2. Complex glycerol kinase deficiency due to contiguous gene deletion		300679
2.5. Disorders of glyoxylate metabolism		
2.5.1. Primary hyperoxaluria type I		260000
2.5.2. Primary hyperoxaluria type II		260000
2.6. Disorders of glucose transport		
2.6.1. Glucose transporter 1 deficiency (blood-brain barrier)		606777
2.6.2. Glucose transporter 2 deficiency		227810
2.6.3. Glucose/galactose malabsorption		606824
2.7. Disorders of gluconeogenesis		
2.7.1. Fructose-1,6-bisphosphatase deficiency		229700
2.7.2. Pyruvate carboxylase deficiency		266150
2.7.3. Phosphoenolpyruvate carboxykinase deficiency	E744	261650
2.8. Glycogen storage disorders		
2.8.1. Glycogen storage disease type 1a		232200
2.8.2. Glycogen storage disease type 1b		232220

2.8.3. Glycogen storage disease type II		232300

Disease group / disease	ICD10	OMIM
2.8.4. Glycogen storage disease type III		232400
2.8.5. Glycogen storage disease type IV		232500
2.8.6. Glycogen storage disease type V		232600
2.8.7. Glycogen storage disease type VI		232700
2.8.8. Glycogen storage disease type VII		232800
2.8.9. Glycogen storage disease type IX		306000
2.8.9.1. Hepatic phosphorylase kinase deficiency		306000
2.8.9.2. Hepatic and muscle phosphorylase kinase deficiency		261750
2.8.9.3. Muscle phosphorylase kinase deficiency		300559
2.8.9.4. Cardiac muscle phosphorylase kinase deficiency		261740
2.8.10. Glycogen storage disease type X		
2.8.11. Glycogen storage disease type XI		227810
2.8.12. Glycogen storage disease type XIV		
2.8.13. Glycogen storage disease type XV		
2.8.14. Glycogen storage disease type 0a		240600
2.8.15. Glycogen storage disease type 0b		611556
2.8.16. Other glycogen storage disease		
2.8.16.1. Muscle LDH deficiency		612933
2.8.16.2. Aldolase A deficiency		611881
2.8.16.3. Beta-enolase deficiency		612932
2.8.16.4. Muscle phosphoglycerate kinase deficiency		300653
2.8.17. Unspecified glycogen storage disease		
2.9. Other carbohydrate disorders		
2.9.1. Lactose intolerance		223000
2.9.2. Disaccharide intolerance 1		222900
2.9.3. Trehalase deficiency		612119
3. Disorders of fatty acid and ketone body metabolism		
3.1. Disorders of lipolysis		
3.2. Disorders of carnitine transport and the carnitine cycle		
3.2.1. Carnitine transporter deficiency	E713	212140
3.2.2. Carnitine palmitoyltransferase I (CPTI) deficiency	E713	255120
3.2.3. Carnitine acylcarnitine translocase deficiency	E713	212138
3.2.4. Carnitine palmitoyltransferase II (CPTII) deficiency	E713	255110
3.3. Disorders of mitochondrial fatty acid oxidation		
3.3.1. Very long - chain acyl CoA dehydrogenase deficiency	E713	201475
3.3.2. Mitochondrial trifunctional protein deficiency	E713	143450
3.3.2.1. Isolated deficiency of long-chain 3-hydroxyacyl-CoA dehydrogenase	E713	143450
3.3.2.2. Isolated deficiency of long-chain 3-ketoacyl CoA thiolase	E713	143450

3.3.3. Medium - chain acyl CoA dehydrogenase deficiency	E713	201450

Disease group / disease	ICD10	OMIM
3.3.4. Short - chain acyl CoA dehydrogenase deficiency	E713	201470
3.3.5. 3-alpha-hydroxyacyl- CoA dehydrogenase deficiency	E713	231530
3.3.6. Multiple acyl-CoA dehydrogenase deficiency	E713	231680
3.3.6.1. Electron transfer flavoprotein deficiency, alpha chain	E713	231680
3.3.6.2. Electron transfer flavoprotein deficiency, beta chain	E713	130410
3.3.6.3. ETF-ubiquinone oxidoreductase deficiency	E713	231675
3.4. Disorders of ketone body metabolism		
3.4.1. 3-Hydroxy-3-Methylglutaryl-CoA synthase deficieny		600234
3.4.2. Succinyl-CoA:3-Oxoacid-CoA transferase (SCOT) deficiency	E798	245050
3.4.3. Cytosolic acetoacetyl-CoA thiolase deficiency	E712	100678
3.5. Other disorders of fatty acid and ketone body metabolism		
3.5.1. Long - chain acyl CoA dehydrogenase deficiency	E713	201460
3.5.2. Malonyl CoA decarboxylase deficiency	E798	248360
4. Disorders of energy metabolism		
4.1. Disorders of pyruvate metabolism		
4.1.1. Pyruvate dehydrogenase complex deficiency		
4.1.1.1. Pyruvate dehydrogenase E1α subunit deficiency		312170
4.1.1.2. Pyruvate dehydrogenase E1β subunit deficiency		179060
4.1.1.3. Dihydrolipoyl transacetylase deficiency		245348
4.1.1.4. Dihydrolipoyl dehydrogenase deficiency		248600
4.1.1.5. Pyruvate dehydrogenase E3 binding protein deficiency		245349
4.1.1.6. Pyruvate dehydrogenase phosphatase deficiency		608782
4.1.1.7. Pyruvate dehydrogenase deficiency, unspecified		312170
4.1.2. Pyruvate kinase deficiency		266200
4.2. Disorders of the citric acid cycle		
4.2.1. 2-Oxoglutarate dehydrogenase deficiency		203740
4.2.2. Fumarase deficiency		136850
4.3. Mitochondrial respiratory chain disorders		
4.3.1. Respiratory chain disorders caused by mutations of mtDNA		
4.3.1.1. Large-scale single deletion of mtDNA		
4.3.1.1.1. Pearson Syndrome		557000
4.3.1.1.2. Kearns Sayre Syndrome		530000
4.3.1.1.3. Chronic Progressive External Ophthalmoplegia (CPEO) with Mitochondrial Myopathy [onset after 20 yrs]		n/a

4.3.1.2. Point mutations of mtDNA		

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4.3.1.2.1. Mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes, MELAS		540000
4.3.1.2.2. Myoclonic epilepsy associated with ragged red fibres, MERRF		545000
4.3.1.2.3. Neuropathy Ataxia and Retinitis Pigmentosa, NARP		551500
4.3.1.2.4. Leber Hereditary Optic Neuropathy, LHON		535000
4.3.1.2.5. Maternally Inherited Leigh Syndrome, MILS		256000
4.3.1.2.6. Sporadic Leigh Syndrome		256000
4.3.1.2.7. Maternally inherited Mitochondrial Dystonia		500001
4.3.1.2.8. Maternally inherited Mitochondrial Cardiomyopathy		n/a
4.3.1.2.9. Maternally inherited Mitochondrial Myopathy		n/a
4.3.1.2.9.1. 'Pure' Mitochondrial Myopathy		n/a
4.3.1.2.9.2. Lethal Infantile Mitochondrial Myopathy		551000
4.3.1.2.9.3. Mitochondrial Myopathy with Diabetes Mellitus		500002
4.3.1.2.9.4. Mitochondrial Myopathy with Reversible cytochrome c oxidase (COX) Deficiency		500009
4.3.1.2.10. Maternally inherited deafness and diabetes, MIDD		520000
4.3.2. Respiratory chain disorders caused by mutations of nuclear DNA		
4.3.2.1. Mitochondrial DNA Depletion Syndromes		
4.3.2.1.1. Alpers-Huttenlocher Syndrome (POLG)		203700
4.3.2.1.2. Hepatocerebral (DGUOK, MPV17, PEO1)		251880
4.3.2.1.3. Myopathic (TK2)		609560
4.3.2.1.4. Encephalomyopathy with methylmalonic aciduria (SUCLA2)		612073
4.3.2.1.5. Fatal Infantile Lactic Acidosis with methylmalonic aciduria (SUCLG1)		245400
4.3.2.1.6. Encephalomyopathic with renal tubulopathy (RRM2B)		612075
4.3.2.1.7. Childhood-onset autosomal dominant optic atophy (OPA1)		165500
4.3.2.1.8. Mitochondrial Neurogastrointestinal Encephalopathy, MNGIE (ECGF1)		603041
4.3.2.2. Multiple mtDNA Deletion Syndromes		
4.3.2.2.1. Progressive External Ophthalmoplegia Autosomal Dominant (PEOA)		
4.3.2.2.1.1. PEOA1 (POLG)		157640

4.3.2.2.1.2. PEOA2 (ANT1)		609283
4.3.2.2.1.3. PEOA3 (PEO1)		609286

Disease group / disease	ICD10	OMIM
4.3.2.2.1.4. PEOA4 (POLG2)		610131
4.3.2.2.1.5. PEOA5 (RRM2B)		613077
4.3.2.2.2. Progressive External Ophthalmoplegia Autosomal Recessive (PEOB)		258450
4.3.2.2.3. Sensory Ataxic Neuropathy, Dysarthria and Ophthalmoparesis, SANDO		607459
4.3.2.2.4. Optic Atrophy 1 and Deafness (OPA1)		125250
4.3.2.3. Leigh Syndrome, LS		256000
4.3.2.3.1. LS with leukodystrophy (SDHA, SURF1)		220110
4.3.2.3.2. LS with cardiomyopathy (COX10, COX15)		220110
4.3.2.3.3. LS with French-Canadian ethnicity (LRPPRC)		220111
4.3.2.3.4. LS with nephrotic syndrome (PDSS2)		607426
4.3.2.3.5. LS with nephropathy (COQ2)		607426
4.3.2.4. Ubiquinone (CoQ10) deficiency (Non-LS)		607426
4.3.2.4.1. Early-onset ataxia with oculomotor apraxia and hypoalbuminaemia (APTX)		607426
4.3.2.4.2. Deafness, encephaloneuropathy, obesity and valvulopathy (PDSS1)		607426
4.3.2.4.3. Cerebellar atrophy, ataxia and seizures (CABC1)		607426
4.3.2.5. Growth Retardation, Aminoaciduria, Cholestasis, Iron overload, Lactic acidosis and Early death (GRACILE) Syndrome (BCS1L)		603358
4.3.2.6. Renal tubulopathy, encephalopathy and liver failure (BCS1L)		124000
4.3.2.7. Cardio-encephalopathy with hyperammonaemia (TMEM70)		604273
4.3.2.8. Exercise Intolerance with Lactic Acidosis		
4.3.2.8.1. Complex I deficiency; riboflavin responsive (ACAD9)		611126
4.3.2.8.2. Complex I and II deficiency (ISCU)		255125
4.3.2.9. Isolated Oxidative Phosphorylation Defects with Variable Phenotype (Not Classified Elsewhere)		
4.3.2.9.1. Complex I structural subunit gene defect (NDUFV1, NDUFV2, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFA1, NDUFA2, NDUFA11)		n/a
4.3.2.9.2. Complex I assembly gene defect (C20orf7, NDUFAF1, NDUFAF2, NDUFAF3, NDUFAF4, C80orf38,		n/a

	NUBPL, FOXRED1)		
4.3.2.9.3.	Complex II structural subunit gene defect (SDHA, SDHB, SDHC,SDHD)		n/a

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4.3.2.9.4.	Complex II assembly gene defect (SDHAF1)		n/a
4.3.2.9.5.	Complex III structural subunit gene defect (UQCRB, UQCRQ)		n/a
4.3.2.9.6.	Complex III assembly gene defect		n/a
4.3.2.9.7.	Complex IV structural subunit gene defect (COX6B1)		n/a
4.3.2.9.8.	Complex IV assembly gene defect (SCO1, SCO2, SURF1, COX10, COX15, TACO1, FASTKD2)		n/a
4.3.2.9.9.	Complex V structural subunit gene defect (ATP5E)		n/a
4.3.2.9.10.	Complex V assembly gene defect (ATPAF2, TMEM70)		n/a
4.3.2.10.	Mitochondrial Protein Translation Defects		
4.3.2.10.1.	Combined Oxidative Phosphorylation Defect 1, COXPD1 (EFG1)		609060
4.3.2.10.2.	Combined Oxidative Phosphorylation Defect 2, COXPD2 (MRPS16)		610498
4.3.2.10.3.	Combined Oxidative Phosphorylation Defect 3, COXPD3 (TSFM)		610505
4.3.2.10.4.	Combined Oxidative Phosphorylation Defect 4, COXPD4 (TUFM)		610678
4.3.2.10.5.	Combined Oxidative Phosphorylation Defect 5, COXPD5 (MRPS22)		611719
4.3.2.10.6.	Combined Oxidative Phosphorylation Defect 6, COXPD6 (AIFM1)		300816
4.3.2.10.7.	Combined Oxidative Phosphorylation Defect 7, COXPD7 (C10ORF65)		613559
4.3.2.10.8.	Myopathy, Lactic Acidosis and Sideroblastic Anaemia 1, MLASA1 (PUS1)		600462
4.3.2.10.9.	Acute Infantile Liver Failure (TRMU)		613070
4.3.2.10.10.	Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation, LBSL (DARS2)		611105
4.3.2.10.11.	Pontocerebellar hypoplasia Type 6 (RARS2)		611523
4.3.2.10.12.	Myopathy, Lactic Acidosis and Sideroblastic Anaemia 2, MLASA2 (YARS2)		613561

4.3.3. Respiratory chain deficiencies with no known genetic basis		
4.3.3.1. Complex I deficiency		252010
4.3.3.2. Complex II deficiency		252011
4.3.3.3. Complex III deficiency		124000

Disease group / disease	**ICD10**	**OMIM**
4.3.3.4. Complex IV deficiency		220110
4.3.3.5. ATP synthase deficiency		604273
4.3.3.6. Combined respiratory chain deficiency		n/a
4.4. Mitochondrial membrane transport disorders		
4.4.1. Mitochondrial substrate carrier disorders		
4.4.1.1. Mitochondrial phosphate carrier deficiency (SLC25A3)		600370
4.4.1.2. Mitochondrial aspartate glutamate carrier 1 deficiency (SLC25A12)		603667
4.4.1.3. Mitochondrial glutamate carrier 1 deficiency (SLC25A22)		609302
4.4.1.4. Mitochondrial carrier SLC25A38, haem biosynthesis, sideroblastic anaemia		610819
4.4.2. Mitochondrial protein import disorders		
4.4.2.1. Mohr-Tranebjaerg syndrome (TIMM8A)		300356
4.5. Unspecified mitochondrial disorders		
4.5.1. Leigh syndrome with no known genetic or respiratory chain deficiency		256000
4.5.2. Ethylmalonic Encephalopathy (ETHE1)		602473
4.5.3. Anaemia, sideroblastic, and spinocerebellar ataxia, ASAT (ABCB7)		301310
4.6. Disorders of creatine metabolism		
4.6.1. Creatine transporter deficiency		
4.6.2. Guanidinoacetate methyltransferase deficiency		612736
4.6.3. Arginine:glycine amidinotransferase deficiency		612718
4.7. Other disorders of energy metabolism		
5. Disorders in the metabolism of purines, pyrimidines and nucleotides		
5.1. Disorders of purine metabolism		
5.1.1. Primary idiopathic gout		138900
5.1.2. Familial juvenile hyperuricaemic nephropathy		162000
5.1.3. Adenylosuccinate lyase deficiency		103050
5.1.4. AICAR transformylase deficiency		601731
5.1.5. Adenosine deaminase deficiency		102700
5.1.6. Deoxyguanosine kinase deficiency		251880
5.1.7. Myoadenylate deaminase deficiency		102770
5.1.8. Lesch-Nyhan syndrome		308000
5.1.9. Adenine phosphoribosyl transferase deficiency		102600
5.1.10. Phosphoribosyl pyrophosphate synthetase 1 defects		311850
5.1.10.1. Phosphoribosyl pyrophosphate synthase		300661

superactivity		
5.1.10.2. X-linked Charcot-Marie-Tooth disease-5		311070
5.1.10.3. Arts syndrome		301835
5.1.10.4. X-linked sensorineural deafness		304500
5.1.11. Inosine triphosphatase deficiency		147520

Disease group / disease	**ICD10**	**OMIM**
5.1.12. Adenosine deaminase superactivity		
5.1.13. Purine nucleoside phosphorylase deficiency		164050
5.1.14. Mitochondrial Ribonucelotide Reductase subunit 2 deficiency		604712
5.1.15. Xanthinuria type I		278300
5.1.16. Xanthinuria type II		603592
5.1.17. Thiopurine S-methyltransferase deficiency		610460
5.2. Disorders of pyrimidine metabolism		
5.2.1. Orotic aciduria type I		258900
5.2.2. Orotic aciduria type II		258920
5.2.3. Pyrimidine - 5 - nucleotidase deficiency		266120
5.2.4. Dihydroorotate dehydrogenase deficiency		263750
5.2.5. Uridine-5'-monophosphate hydrolase superactivity		266120
5.2.6. Thymidine phosphorylase deficiency		131222
5.2.7. Thymidine kinase 2 deficiency		609560
5.2.8. Dihydropyrimidine dehydrogenase deficiency		274270
5.2.9. Dihydropyrimidinase deficiency		222748
5.2.10. Beta-ureidopropionase deficiency		613161
5.2.11. Hyper-beta-alaninaemia		237400
5.2.12. Beta-aminoisobutyrate-pyruvate transaminase deficiency		210100
5.3. Disorders of nucleotide metabolism		
5.3.1. Aicardi-Goutières Syndrome (AGS)		
5.3.1.1. AGS1		225750
5.3.1.2. AGS2		610181
5.3.1.3. AGS3		610181
5.3.1.4. AGS4		610181
5.3.1.5. AGS5		612952
5.3.2. RNASET2-deficient cystic leukoencephalopathy		612951
6. Disorders of the metabolism of sterols		
6.1. Disorders of sterol biosynthesis		
6.1.1. Mevalonate kinase deficiency		610377
6.1.2. Smith - Lemli - Opitz syndrome	Q871	270400
6.1.3. X-linked dominant chondrodysplasia punctata 2		302960
6.1.4. Congenital hemidysplasia with ichtyosiform erythroderma and limb defects		308050
6.1.5. Desmosterolosis		602398

6.1.6. Lathosterolosis		607330
6.1.7. Greenberg skeletal dysplasia		215140
6.2. Disorders of bile acid biosynthesis		
6.2.1. 3- β-hydroxysterol Δ5-oxidoreductase/isomerase deficiency		
6.2.2. Δ4-3-oxysterol 5β-reductase deficiency		

Disease group / disease	**ICD10**	**OMIM**
6.2.3. Oxysterol 7-alpha-hydroxylase		
6.2.4. Cholesterol 7-alpha-hydroxylase		
6.2.5. Cerebrotendinous xanthomatosis		213700
6.3. Disorders of bile acid metabolism and transport		
6.3.1. Bilirubin UDP-glucuronosyltransferase 1 deficiency		
6.3.2. Byler disease		
6.3.3. Progressive familial intrahepatic cholestasis type 2		
6.3.4. Progressive familial intrahepatic cholestasis type 3		
6.4. Other disorders in the metabolism of sterols		
6.4.1. X-linked ichthyosis		308100
7. Disorders of porphyrin and haem metabolism		
7.1.1. Erythropoietic porphyria		177000
7.1.2. X-linked dominant protoporphyria		300752
7.1.3. Variegate porphyria		176200
7.1.4. X-linked sideroblastic anaemia (XLSA)		300751
7.1.5. Congenital erythropoietic porphyria		263700
7.1.6. Acute intermittent porphyria		176000
7.1.7. Hereditary coproporphyria		121300
7.1.8. Porphyria cutanea tarda type I (sporadic)		176090
7.1.9. Porphyria cutanea tarda type II (familial)		176100
7.1.10. Acute hepatic porphyria		612740
8. Disorders of lipid and lipoprotein metabolism		
8.1. Inherited hypercholesterolaemias		
8.1.1. Disorder of low density lipoprotein receptor	E780	143890
8.1.1.1. Familial hypercholesterolaemia - homozygous	E780	
8.1.1.2. Familial hypercholesterolaemia - heterozygous	E780	
8.1.2. Sitosterolaemia	E755	210250
8.2. Inherited hypertriglyceridaemias		
8.2.1. Familial chylomicronaemia	E786	238600
8.2.1.1. Familial lipoprotein lipase deficiency	E786	238600
8.2.1.2. Familial apolipoprotein C - II deficiency	E786	207750
8.2.2. Familial hypertriglyceridaemia	E786	238600
8.3. Inherited mixed hyperlipidaemias		
8.3.1. Familial dysbetalipoproteinaemia	E782	107741
8.3.1.1. Dysfunctional apo E		

8.3.2. Familial combined hyperlipoproteinaemia		
8.3.3. Hepatic lipase deficiency		
8.4. Disorders of high density lipoprotein metabolism		
8.4.1. Apolipoprotein A-I deficiency	E786	
8.4.2. Tangier disease	E786	205400
8.4.3. Lecithin cholesterol acyltransferase deficiency		

Disease group / disease	**ICD10**	**OMIM**
8.4.3.1. Fish-eye disease	E786	136120
8.4.3.2. Norum disease	E786	245900
8.4.4. Familial hyperalphalipoproteinaemia		
8.5. Inherited hypolipidaemias		
8.5.1. Familial abetalipoproteinaemia	E786	200100
8.5.2. Familial hypobetalipoproteinaemia	E786	200100
8.5.3. Anderson disease		
8.6. Other disorders of lipid and lipoprotein metabolism		
8.6.1.1. Sjøgren - Larsson syndrome	Q898	270200
8.6.1.2. Pancreatic triacylglycerol lipase deficiency	E888	246600
8.6.1.3. Pancreatic colipase deficiency	E755	120105
8.7. Unspecified disorders of lipid and lipoprotein metabolism		
9. Congenital disorders of glycosylation and other disorders of protein modification	E778	
9.1. Disorders of protein N-glycosylation		
9.1.1. Phosphomannomutase 2 deficiency	E744	601785
9.1.2. Phosphomannose isomerase deficiency	E778	602579
9.1.3. Glucosyltransferase 1 deficiency	E744	603147
9.1.4. Mannosyltransferase 6 deficiency	E744	601110
9.1.5. Mannosyltransferase 8 deficiency	E744	607143
9.1.6. Glucosyltransferase 2 deficiency	E744	608104
9.1.7. Mannosyltransferase 2 deficiency		607906
9.1.8. UDP-GlcNAc:Dol-P-GlcNac-P transferase deficiency		608093
9.1.9. Mannosyltransferase 1 deficiency		608540
9.1.10. Mannosyltransferase 7-9 deficiency		608776
9.1.11. Flippase of Man5GlcNAc2-PP-Dol deficiency		611633
9.1.12. N-acetylglucosaminyltransferase deficiency		602616
9.1.13. Glucosidase 1 deficiency		606056
9.1.14. TUSC3-CDG		601385
9.1.15. SRD5A3-CDG		
9.2. Disorders of protein O-glycosylation	E744	
9.2.1. O-xylosylglycan synthesis deficiencies		
9.2.1.1. EXT1 deficiency		608177
9.2.1.2. EXT2 deficiency		608210
9.2.1.3. Beta-1,4-galactosyltransferase 7 deficiency		604327

9.2.2. O-N-acetylgalactosaminylglycan synthesis deficiencies		
9.2.2.1. Polypeptide N-acetylgalactosaminyl transferase deficiency		601756
9.2.3. O-xylosyl/N-acetylgalactosaminylglycan synthesis deficiencies		
9.2.3.1. SLC35D1 deficiency		610804
9.2.4. O-mannosylglycan synthesis deficiencies		
9.2.4.1. Protein-O-mannosyltransferase 1 deficiency		607423

Disease group / disease	**ICD10**	**OMIM**
9.2.4.2. Protein-O-mannosyltransferase 2 deficiency		607423
9.2.4.3. Protein-O-mannose beta-1,2-N-acetyglucosaminyltransferase deficiency	E744	606822
9.2.4.4. Fukutin deficiency	E744	607440
9.2.4.5. Fukutin-related protein deficiency		606596
9.2.4.6. N-acetylglucosaminyltransferase-like protein deficiency		603590
9.2.4.7. O-fucose-specific beta-1,3-N-acetylglucosaminyltransferase deficiency		602576
9.2.4.8. O-fucose-specific beta-1,3-N-glucosyltransferase deficiency		610308
9.3. Disorders of glycosphingolipid and glycosylphosphatidylinositol anchor glycosylation		
9.3.1.1. Lactosylceramide alpha-2,3-sialyltransferase deficiency		609056
9.3.1.2. Phosphatidylinositolglycan, class M deficiency		610273
9.4. Disorders of multiple glycosylation and other glycosylation pathways		
9.4.1. GDP-Man:Dol-P mannosyltransferase deficiency		603503
9.4.2. Lec35 deficiency		608799
9.4.3. Beta-1,4-galactosyltransferase 1 deficiency		607091
9.4.4. UDP-GlcNAc epimerase/kinase deficiency		600737
9.4.5. CMP-sialic acid transporter deficiency		605634
9.4.6. GDP-fucose transporter deficiency		605881
9.4.7. Dolichol pathway deficiencies		
9.4.7.1. Dolichol kinase deficiency		610768
9.4.8. Conserved oligomeric Golgi (COG) complex deficiency		
9.4.8.1. Component of COG complex 7 deficiency		606978
9.4.8.2. Component of COG complex 1 deficiency		606973
9.4.8.3. Component of COG complex 8 deficiency		606979
9.4.9. V-ATPase deficiencies		
9.4.9.1. V0 subunit A2 of vesicular H(+)-ATPase deficiency		611716
9.5. Disorders of protein ubiquitinylation		
9.6. Other disorders of protein modification		
10. Lysosomal disorders		
10.1. Mucopolysaccharidoses	E76.	

10.1.1. MPS I, Hurler, Scheie disease	E76.0	252800
10.1.2. MPS II, Hunter disease	E76.1	309900
10.1.3. MPS IIIA, Sanfilippo A disease	E76.2	252900
10.1.4. MPS IIIB, Sanfilippo B disease	E76.2	252920
10.1.5. MPS IIIC, Sanfilippo C disease	E76.2	252930
10.1.6. MPS IIID, Sanfilippo D disease	E76.2	252940
10.1.7. MPS IVA, Morquio A disease	E76.2	253000
10.1.8. MPS IVB, Morquio B disease	E76.2	253010

Disease group / disease	**ICD10**	**OMIM**
10.1.9. MPS VI, Maroteaux - Lamy disease	E76.2	253200
10.1.10. MPS VII, Sly disease	E76.2	253220
10.1.11. MPS IX	E76.2	601492
10.2. Oligosaccharidoses	E77.0	
10.2.1. Aspartylglucosaminuria	E77.1	208400
10.2.2. Fucosidosis	E77.1	230000
10.2.3. Alpha - D – mannosidosis	E77.1	248500
10.2.4. Beta - D – mannosidosis	E77.1	248510
10.2.5. Schindler disease	E77.1	104170
10.2.5.1. Schindler disease type I	E77.1	104170
10.2.5.2. Kanzaki disease	E77.1	104170
10.2.6. Sialidosis	E77.1	256550
10.3. Sphingolipidoses	E75.0	
10.3.1. GM1-gangliosidosis	E75.1	230500
10.3.2. GM2-gangliosidosis	E75.0	268800
10.3.2.1. GM2-gangliosidosis 0-variant,	E75.0	268800
10.3.2.2. GM2-gangliosidosis B-variant	E75.0	272800
10.3.2.3. GM2-gangliosidosis AB-variant	E75.0	272750
10.3.3. Gaucher disease	E75.2	230800
10.3.4. Krabbe disease	E75.2	245200
10.3.5. Metachromatic leukodystrophy		250100
10.3.6. Prosaposin deficiency	E75.2	176801
10.3.6.1. Saposin A deficiency	E75.2	611722
10.3.6.2. Saposin B deficiency	E75.2	249900
10.3.6.3. Saposin C deficiency	E75.2	610539
10.3.6.4. Saposin D deficiency		
10.3.7. Fabry disease	E75.2	301500
10.3.8. Farber disease	E75.2	228000
10.3.9. Niemann-Pick disease type A or B	E75.2	257200
10.3.10. Niemann-Pick disease type C	E75.2	257220
10.3.10.1. Niemann-Pick disease type C1	E75.2	257220
10.3.10.2. Niemann-Pick disease type C2	E75.2	607625
10.4. Ceroid lipfuscinoses, neuronal (CLN)		

10.4.1. CLN1, Santavuori-Haltia disease	E75.4	256730
10.4.2. CLN2, Jansky-Bielschowsky disease	E75.4	204500
10.4.3. CLN3, Batten Spielmeyer-Vogt disease	E75.4	204200
10.4.4. CLN4A, Kufs disease recessive type	E75.4	204300
10.4.5. CLN4B Kufs disease dominant type	E75.4	162350
10.4.6. CLN5 Finnish variant	E75.4	256731
10.4.7. CLN6	E75.4	601780
10.4.8. CLN7	E75.4	610950

Disease group / disease	**ICD10**	**OMIM**
10.4.9. CLN8, Northern epilepsy type	E75.4	600143
10.4.10. CLN9	E75.4	609055
10.4.11. CLN10	E75.4	610127
10.5. Lysosomal export disorders		
10.5.1. Cystinosis	E72.0	219800
10.5.2. Salla disease/infantile sialic acid storage disease		269920
10.6. Other lysosomal disorders		
10.6.1. Mucolipidosis II, I-cell disease	E77.0	252500
10.6.2. Mucolipidosis III, Pseudo-Hurler polydystrophy	E77.0	252605
10.6.3. Mucolipidosis IV	E75.1	252650
10.6.4. Multiple sulphatase deficiency	E76.2	272200
10.6.5. Wolman/cholesterol ester storage disease	E75.5	278000
10.6.6. Pompe disease, GSD type II	E74.0	232300
10.6.7. Sialuria		269921
10.6.8. Danon disease		300257
10.6.9. Cathepsin-related disorders		265800
10.6.9.1. Galactosialidosis	E77.1	256540
10.6.9.2. Papillon-Lefèvre syndrome		245000
10.6.9.3. Pycnodysostosis		265800
10.6.10. Hermansky-Pudlak Syndrome	E70.3	203300
11. Peroxisomal disorders		
11.1. Disorders of peroxisome biogenesis		
11.1.1. Zellweger spectrum disorder, severe form		214100
11.1.2. Zellweger spectrum disorder, attenuated form		214100
11.1.2.1. Neonatal adrenoleukodystrophy		202370
11.1.2.2. Infantile Refsum disease		266510
11.1.3. Zellweger spectrum disorder, unclassified clinical severity		214100
11.1.3.1. PEX1 deficiency		602136
11.1.3.2. PEX2 deficiency		170993
11.1.3.3. PEX3 deficiency		603164
11.1.3.4. PEX5 deficiency		600414
11.1.3.5. PEX6 deficiency		601498

11.1.3.6. PEX10 deficiency		602859
11.1.3.7. PEX12 deficiency		601758
11.1.3.8. PEX13 deficiency		601789
11.1.3.9. PEX14 deficiency		601791
11.1.3.10. PEX16 deficiency		603360
11.1.3.11. PEX19 deficiency		600279
11.1.3.12. PEX26 deficiency		608666
11.2. Rhizomelic chondrodysplasia punctata		
11.2.1. Rhizomelic chondrodysplasia punctata type 1		215100

Disease group / disease	**ICD10**	**OMIM**
11.2.2. Rhizomelic chondrodysplasia punctata type 2		222765
11.2.3. Rhizomelic chondrodysplasia punctata type 3		600121
11.3. Disorders of peroxisomal alpha-, beta and omega-oxidation		
11.3.1. X-linked adrenoleukodystrophy		300100
11.3.2. Peroxisomal acyl-CoA oxidase 1 deficiency		264470
11.3.3. Peroxisomal D-bifunctional protein deficiency		261515
11.3.4. Sterol carrier protein deficiency		
11.3.5. Alpha-methylacyl-CoA racemase deficiency		604489
11.3.6. Refsum disease		266500
11.4. Other peroxisomal disorders		
11.4.1. Primary hyperoxaluria type I		259900
11.4.2. Acatalasaemia		115500
12. Disorders of neurotransmitter metabolism		
12.1. Disorders in the metabolism of biogenic amines		
12.1.1. Tyrosine hydroxylase deficiency		191290
12.1.2. Aromatic L-amino acid decarboxylase deficiency	E728	608643
12.1.3. Dopamine beta-hydroxylase deficiency	E250	223360
12.2. Disorders in the metabolism of gamma-aminobutyrate		
12.2.1. Succinic semialdehyde dehydrogenase deficiency	E722	271980
12.2.2. GABA transaminase deficiency	E728	137150
12.3. Other disorders of neurotransmitter metabolism		
13. Disorders in the metabolism of vitamins and (non-protein) cofactors		
13.1. Disorders of folate metabolism and transport		
13.1.1. Hereditary folate malabsorption	E538	229050
13.1.2. Cerebral folate deficiency due to FOLR1 deficiency	-	613068
13.1.3. Methylenetetrahydrofolate reductase deficiency	E711	236250
13.1.4. Other genetic disorders in folate transport and metabolism	D528	-
13.1.5. Unspecified disorders of folate transport and metabolism	D528	-
13.1.6. Secondary disorders of folate transport and metabolism	D529	-

13.1.7. Cerebral folate deficiency due to autoantibodies-non-genetic	-	-
13.2. Disorders of cobalamin absorption, transport and metabolism		
13.2.1. Intrinsic factor deficiency	D510	609342
13.2.2. Enterocyte intrinsic factor receptor deficiency	D511	261100
13.2.2.1. Intrinsic factor receptor deficiency due to CUBN mutations	D511	602997
13.2.2.2. Intrinsic factor receptor deficiency due to AMN mutations	D512	605799
13.2.3. Haptocorrin deficiency	D512	189905

Disease group / disease	**ICD10**	**OMIM**
13.2.4. Transcobalamin II deficiency	D512	275350
13.2.5. Defect in adenosylcobalamin synthesis-cbl A	E711	251100
13.2.6. Defect in adenosylcobalamin synthesis-cbl B	E711	251110
13.2.7. Defect in adenosylcobalamin synthesis-cblD-MMA	E728	277410
13.2.8. Defect in methylcobalamin synthesis-cblD-HC	E728	277410
13.2.9. Combined defect in adenosylcobalamin and methylcobalamin synthesis-cblC	E728	277400
13.2.10. Combined defect in adenosylcobalamin and methylcobalamin synthesis-cblD	E728	277410
13.2.11. Combined defect in adenosylcobalamin and methylcobalamin synthesis-cblF	E728	277380
13.2.12. Transcobalamin receptor (TCblR/CD320) defect		606475
13.2.13. Other genetic defect in cobalamin transport and metabolism	D518	-
13.2.14. Unspecified disorder of cobalamin absorption, transport and metabolism	D518	-
13.2.15. Secondary non-genetic disorders of cobalamin absorption, transport and metabolism	D518	-
13.3. Disorders of pterin metabolism	E701	
13.3.1. Guanosine 5 triphosphate cyclohydrolase I deficiency	E701	233910
13.3.2. 6-Pyruvoyl-tetrahydropterin synthase deficiency	E744	261640
13.3.3. Sepiapterin reductase deficiency	E701	612716
13.3.4. Quinoid dihydropteridine reductase deficiency	E744	261630
13.3.5. Pterin 4 carbinolamine dehydratase deficiency	E888	125310
13.4. Disorders of vitamin D metabolism and transport		
13.5. Disorders of biotin metabolism		
13.5.1. Biotinidase deficiency	D818	253260
13.5.2. Holocarboxylase synthetase deficiency		253270
13.6. Disorders of pyridoxine metabolism		
13.6.1. Pyridoxine-dependent seizures		266100
13.6.2. Pyridoxamine 5´-oxidase deficiency	E531	610090
13.7. Disorders of thiamine metabolism		
13.7.1. Thiamine-responsive megaloblastic anemia syndrome	E519	249270
13.7.2. Biotin-responsive basal ganglia disease		607483

13.7.3. Microcephaly, Amish type		607196
13.8. Disorders of molybdenum cofactor metabolism		
13.8.1. Molybdenum cofactor deficiency	E798	252150
13.8.1.1. Mo cofactor deficiency, complementation group A	E798	603707
13.8.1.2. Mo cofactor deficiency, complementation group B	E798	603708
13.8.1.3. Mo cofactor deficiency, complementation group C	E798	603930
13.9. Other disorders of vitamins and cofactors		
13.9.1. TTP1 deficiency	E560	277460
13.9.2. Vitamin K epoxide reductase deficiency	E561	607473
13.9.3. Retinol binding protein deficiency	E509	180250

Disease group / disease	**ICD10**	**OMIM**
13.9.4. Pantothenate kinases deficiency	E568	234200
14. Disorders in the metabolism of trace elements and metals		
14.1. Disorder of copper metabolism	E830	
14.1.1. Menkes syndrome	E830	309400
14.1.2. Occipital horn syndrome	Q796	304150
14.1.3. Wilson disease	E830	277900
14.2. Disorder of iron metabolism	E831	
14.2.1. Hereditary haemochromatosis		
14.2.1.1. Hereditary haemochromatosis Type 1	E831	235200
14.2.1.2. Hereditary haemochromatosis Type 2	E831	235200
14.2.1.3. Hereditary haemochromatosis Type 3	E831	235200
14.2.1.4. Hereditary haemochromatosis Type 4	E831	235200
14.2.2. Neonatal haemochromatosis	E831	
14.2.3. Haemosiderosis, acquired	E831	
14.3. Disorder of zinc metabolism	E832	
14.3.1. Acrodermatitis enteropathica	E832	201100
14.3.2. Hyperzincemia and hypercalprotectinemia	E832	194470
14.4. Disorder of phosphate, calcium and vitamin D metabolism	E835	
14.5. Disorder of magnesium metabolism	E834	
14.5.1. Hypermagnesaemia	E834	
14.5.2. Hypomagnesaemia	E834	
14.5.3. Primary hypomagnesaemia	E834	
14.5.3.1. Isolated familial renal hypomagnesaemia	E834	
14.5.3.2. Familial hypokalaemia - hypomagnesaemia	E876	
14.5.3.3. Familial hypomagnesaemia - hypercalciuria	E888	
14.5.3.4. Isolated familial intestinal hypomagnesaemia	E834	
14.5.4. Secondary hypomagnesaemia	E834	
14.5.4.1. Neonatal hypomagnesaemia	P712	307600
14.5.4.2. Hypomagnesaemic tetany in newborn	P713	
14.5.4.3. Drug induced hypomagnesaemia	E834	
14.5.5. Hypomagnesaemic tetany	E834	

14.6. Disorders in the metabolism of other trace elements and metals		
15. Disorders and variants in the metabolism of xenobiotics		
15.1. Disorders and variants of cytochrome P450-mediated oxidation		
15.2. Disorders and variants of other enzymes that oxidise xenobiotics		
15.2.1. Trimethylaminuria	E888	602079
15.3. Disorders and variants of xenobiotics conjugation		
15.4. Disorders and variants of xenobiotics transport		
16.0 Inborn Errors otherwise unspecified		