synlab Medizinisches
Versorgungszentrum
Humane Genetik Munich

Index of Analyses

2nd edition

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Imprint

Our laboratory is part of the synlab group.

We reserve the right for errors and alterations.

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Medical Practice and Laboratory for Human genetics

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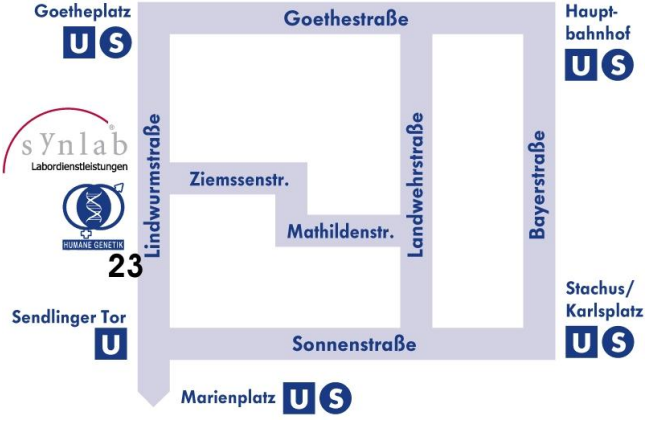
Goetheplatz
Goethestraße
Haupt-
bahnhof
synlab
Labordienstleistungen
HUMANE GENETIK
23
Lindwurmstraße
Ziemssenstr.
Mathildenstr.
Landwehrstraße
Bayerstraße
Stachus/
Karlsplatz
Sendlinger Tor
Sonnenstraße
Marienplatz

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Pre-Analytics

Testing Material

For genetic testing nuclei-containing cells of the patient are required, from which DNA will be isolated. Cells can be harvested from peripheral blood, buccal swabs, amniotic fluid, chorionic villi (CVS), or tissue samples.

In case of blood collection, no special preparation of the patient, e.g. fasting, is required. The sample may be collected at any time of the day.

The blood collection must be performed under sterile conditions. The tubes should always be filled up to the measure line to guarantee an optimal ratio between blood and anticoagulants. Please invert the tubes carefully after blood collection to allow adequate mixing of blood and anticoagulants.

Blood samples should not be older than one week. Please make sure that the samples are sent to our laboratory immediately at room temperature, and avoid extreme temperatures during the transport.

Cytogenetic and Molecular Cytogenetic Analyses

5 ml sterile heparin blood (infants and young children < 5 ml)
10-15 ml amniotic fluid
10-20 mg chorionic villi (CVS)
Abort material with chorionic villi (CVS)
Skin biopsy
Buccal swab

Array-CGH:

3-5 ml freshly collected EDTA-blood, or 2 µg high quality DNA.
In case of a conspicuous finding, 3-5 ml heparin blood is needed for validation of the result by FISH-analysis.

For verification of a conspicuous finding: EDTA-blood or 2 µg high quality DNA, and heparin blood of the parents

Molecular Genetic Analyses

5 ml EDTA-blood (infants and young children < 3 ml)
Amniotic fluid
Chorionic villi (CVS)
Abort material
Tissue
Skin biopsy
Buccal swabs

In general, EDTA-blood is the most suitable material for molecular genetic analyses. Please inquire if other genetic material is suitable for the requested analysis if blood collection is not possible.

Paternity and Kinship Analysis

3 x buccal swabs or 3-5 ml EDTA-blood

Sample Identification and Required Forms

Sample tubes and the corresponding request forms must be clearly labelled with the patient's name and date of birth for correct identification.

Our request forms are available for download at www.humane-genetik.de/formulardownload2.html

Please state the indication for the requested analysis. A short anamnesis as well as family history will significantly support our experts in performing the optimal analysis and for the assessment of the findings.

According to German law, the informed consent form must be signed either by the patient (or his/her legal representative) or by the referring physician. This form is mandatory for every genetic analysis and must be sent together with the sample and the request forms. Informed consent paternity!

Prepayment. Prices available on request.

Leinfelden procedure

Form E112

The spectrum of our genetic analyses is continually expanding. An updated version of the genetic analyses we currently offer can be accessed on our website: www.humane-genetik.de.

Genetic analyses not offered by our laboratory can be performed in co-operation with other accredited laboratories. Please inquire.

Molecular Genetic Analyses

Anemia:

α-Thalassemia

OMIM: 141800

- Genes: *HBA1*, *HBA2*, locus 16pter-p13.3
- Inheritance: autosomal recessive
- Indication: microcytic hypochromic anemia
- TAT: approx. 2-3 weeks
- Methods:
  1st tier: large deletion/duplication analysis (MLPA) of *HBA1* and *HBA2*
  2nd tier: PCR and sequencing analysis of *HBA1* and *HBA2*

β – Thalassemia

OMIM: 141900

- Gene: *HBB*, locus 11p15.5
- Indication: microcytic hypochromic anemia, increased amounts of hemoglobin A2 (HbA2) and F (HbF)
- TAT: approx. 2-3 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *HBB*
  2nd tier: large deletion/duplication analysis (MLPA) of *HBB*

Sickle Cell Anemia

OMIM: 603903

- Gene: *HBB*, locus 11p15.5
- Inheritance: autosomal recessive
- Indication: suspected sickle cell anemia
- TAT: 3-5 days
- Method: Real-time-PCR (LightCycler technique), detection of the mutations HbS and HbC

Glucose-6-Phosphate Dehydrogenase Deficiency

OMIM: 305900

- Gene: *G6PD*, locus Xq28
- Inheritance: X-linked recessive
- Indication: Anemia (nonspherocytic hemolytic anemia), hemolytic episodes, Favism
- TAT: approx. 2 weeks
- Method: PCR and sequencing analysis of *G6PD*

Immune disorders:

HLA-B27 genotyping

OMIM: 142800

- Gene: Major Histocompatibility Complex, locus 6p21.3
- Indication: autoimmune diseases, e. g. suspected Bechterew disease
- TAT: approx. 2 days - 1 week
- Method: sequence specific PCR (SSP)

Cardiac arrhythmic disorders

Brugada syndrome, BrS1

OMIM: 601144

- Gene: *SCN5A,*locus 3p21-23
- Inheritance: usually autosomal dominant, variable penetrance
- Indication: ECG anomalies (T-wave alternans, QT-segment elevation), syncope, absence of structural cardiac disease, family history of sudden cardiac death.
- TAT: approx. 2-3 weeks
- Method: PCR and sequencing analysis of *SCN5A*

Long QT syndrome (LQT1, LQT2, LQT3, LQT5, LQT6)

OMIM: 192500, 613688, 603830, 613695, 613693

- Genes: *KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2*, loci 11p15.5, 7q35-36, 3p21-23, 21q22.1-22.2
- Inheritance: usually autosomal dominant, variable penetrance

- Indication: ECG anomalies (prolongation of the QTc-interval, T-wave abnormalities), syncope, absence of structural cardiac disease, family history of sudden cardiac death.
- TAT: approx. 3-4 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *KCNQ1, KCNH2, SCN5A, KCNE1* and *KCNE2*
  2nd tier: large deletion/duplication analysis (MLPA) of *KCNQ1, KCNH2, KCNE1* and *KCNE2*

Short QT syndrome (SQT1, SQT2)

OMIM: 609620, 609621

- Genes: *KCNH2, KCNQ1,* loci 7q35-36, 11p15.5
- Inheritance: usually autosomal dominant, variable penetrance
- Indication: short QTc-interval in ECG, ventricular fibrillation, syncope, absence of structural cardiac disease, family history of sudden cardiac death.
- TAT: approx. 2-3 weeks
- Method: PCR and sequencing analysis of *KCNH2* and *KCNQ1*

Complex syndromes

Aarskog syndrome (Faciogenital Dysplasia)

OMIM: 305400

- Gene: *FGD1*, locus Xp11.21
- Inheritance: X-linked recessive
- Indication: suspected faciogenital Dysplasia, short stature, hypertelorism, shawl scrotum, and brachydactyly
- TAT: approx. 2-3 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *FGD1*
  2nd tier: large deletion/duplication analysis (MLPA) of *FGD1*

Angelman syndrome (AS)

OMIM: 105830

- Gene: *SNRPN*-gene locus; *UBE3A*-gene, Locus 15q11-13

- Indication: severe mental retardation with profound speech impairment, gait ataxia and/or tremulousness of the limbs, unique behaviour with an inappropriate happy demeanour, microcephaly and seizures, hypotonia,
- TAT: approx. 2-3 weeks
- Methods:
  1st tier: methylation sensitive deletion/duplication analysis (MS-MLPA) *SNRPN*-gene locus
  2nd tier (for inconspicuous result from MS-MLPA): PCR and sequencing analysis of *UBE3A*
  3rd tier (for conspicuous result from MS-MLPA): uniparental disomy 15 (UPD15) analysis (parents' sample required)

Beckwith-Wiedemann syndrome (BWS)

OMIM: 130650

- Gene *H19*-/ *KCNQ1OT1*-gene locus; locus 11p15.5
- Indication: macrosomia (large body size), macroglossia, visceromegaly, embryonal tumors (e.g., Wilms tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma), omphalocele, neonatal hypoglycemia, ear creases/pits, adrenocortical cytomegaly, renal abnormalities (e.g., medullary dysplasia, nephrocalcinosis, medullary sponge kidney, and nephromegaly).
- TAT: approx. 1-2 weeks
- Methods:
  1st tier: methylation sensitive deletion/duplication analysis (MLPA)
  2nd tier (for conspicuous result from MS-MLPA): uniparental disomy 11 (UPD11) analysis (parents' sample required)

DiGeorge syndrome

OMIM: 188400

- Loci: 22q11.2, 10p14 (*DGS2*)
- Inheritance: autosomal dominant
- Indication: congenital heart disease, particularly conotruncal malformations (tetralogy of Fallot, interrupted aortic arch, ventricular septal defect, and truncus arteriosus); palatal abnormalities , particularly velopharyngeal incompetence (VPI), submucosal cleft palate, and cleft palate, hypocalcemia
- TAT: approx. 1 week
- Method: large deletion/duplication analysis (MLPA) of DiGeorge region

Fragile X syndrome (Martin-Bell syndrome, FraX-A)

OMIM: 309550

- Gene: *FMR1*, locus Xq27.3
- Inheritance: X-linked
- Indication: mental retardation particularly in males, incidence 1:1250, determination of carrier status in members of risk families, clinical suspicion of premature ovarian failure (POI) or FraX-associated tremor/ataxia syndrome
- TAT: approx. 2 weeks, prenatal analysis: approx. 1 week
- Methods: fragment analysis and Southern Blot analysis for the determination of the CGG-repeat length in the promotor region of *FMR1*

Fragile X syndrome (FraX-E)

OMIM: 309548

- Gene: *FMR-2,* Locus Xq28
- Inheritance: X-linked
- Indication: mental retardation particularly in males, analysis of the carrier status in families with positive family history for Fragile X-syndrome
- TAT: approx. 2 weeks, prenatal analysis: approx. 1 week
- Methods: fragment analysis and Southern Blot analysis for the determination of the GCC-repeat length in the *FMR2* gene

HDR (Hypoparathyroidism, Sensorineural Deafness, and Renal Disease) syndrome

OMIM: 146255

- Gene: *GATA3*-gene, locus 10p15
- Inheritance: autosomal dominant
- Indication: hypocalcemia, tetany, hearing loss (usually bilateral ranging from mild to profound impairment), renal disease manifestations: nephrotic syndrome, cystic kidney, renal dysplasia, hypoplasia or aplasia, pelvicalyceal deformity, vesicoureteral reflux, chronic renal failure, hematuria, proteinuria and renal scarring.
- TAT: approx. 1-2 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *GATA3*
  2nd tier: large deletion/duplication analysis (MLPA) of *GATA3*

Kallmann syndrome

OMIM: 308700, 147950

- Gene: *KAL1, FGFR1,* loci Xp22.3, 8p11.2-p11.1

- Inheritance: X-linked recessive (*KAL1*), autosomal dominant (*FGFR1*)
- Indication: idiopathic or isolated hypogonadotropic hypogonadism (IHH) and anosmia or hyposmia
- TAT: approx. 2-3 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *KAL1* and *FGFR1*
  2nd tier: large deletion/duplication analysis (MLPA) of *KAL1* and *FGFR1*

LEOPARD syndrome

OMIM: 151100

- Gene: *PTPN11,* locus 12q24.1
- Inheritance: autosomal dominant
- Indication: LEOPARD = lentiginosis, ECG-abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retarded growth, deafness
- TAT: approx. 2 weeks
- Method:
  1st tier:PCR and sequencing analysis of exons 7, 12 und 13 *PTPN11*
  2nd tier: PCR and sequencing analysis of exons 1-6, 8-11, 14 *PTPN11*

Noonan syndrome

OMIM: 163950, 610733

- Genes: *PTPN11, SOS1,* loci 12q24.1, 2p22-p21
- Inheritance: autosomal dominant
- Indication: congenital heart defect, pulmonary stenosis, cardiac hypertrophy, short stature, triangular shaped face, hypertelorism, cryptorchidism, in some cases slight mental retardation
- TAT: approx. 2 weeks
- Method:
  1st tier: PCR and sequencing analysis of exons 3, 7, 8 *PTPN11*
  2nd tier: PCR and sequencing analysis *SOS1*
  3rd tier: PCR and sequencing analysis exons 1-2, 4-6, 9-12, 14, 15 *PTPN11*

Prader-Willi syndrome (PWS)

OMIM: 176270

- Gene: *SNRPN*, locus 15q11-13
- Indication: severe hypotonia and feeding difficulties in early infancy, followed in later infancy or early childhood by excessive eating and

gradual development of morbid obesity, delayed motor milestones and language development, cognitive impairment, hypogonadism and genital hypoplasia, analysis of carriership in families with positive family history of Prader-Willi syndrome
- TAT: approx. 2 weeks
- Methods:
- 1st tier: methylation sensitive deletion/duplication analysis (MLPA) *SNRPN* locus
- 2nd tier (for conspicuous result from MS-MLPA): uniparental disomy 15 (UPD15) analysis (parents' sample required)

Rett syndrome

OMIM: 312750
- Gene: *MECP2*, locus Xq28
- Inheritance: X-linked dominant
- Indication: mental retardation particularly in females, normal psychomotor development during the first six to 18 months of life, followed by a short period of developmental stagnation, then rapid regression in language and motor skills, autism, repetitive, stereotypic hand movements
- TAT: approx. 2 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *MECP2*
  2nd tier: large deletion/duplication analysis (MLPA) of *MECP2*

Silver-Russell syndrome (SRS)

OMIM: 180860
- Gene: *H19-/ IGF2*-gene locus; locus 11p15.5
- Indication: intrauterine growth retardation accompanied by postnatal growth deficiency, proportionately short stature, normal head circumference, fifth-finger clinodactyly, typical facial features and limb-length asymmetry that may result from hemihypotrophy
- TAT: approx. 2 weeks
- Methods:
  1st tier: methylation sensitive deletion/duplication analysis (MLPA) *H19-/IGF2*-gene locus
  2nd tier: uniparental disomy 7(UPD7 analysis) (parents' sample required)

Sotos syndrome

OMIM: 117550

- Gene: *NSD1*-gene, locus 5q35
- Inheritance: autosomal dominant
- Indication: typical facial appearance, macrocephaly, overgrowth (height and head circumference ≥2 SD above the mean), learning disability ranging from mild to severe
- TAT: approx. 1 week
- Method:
  1st tier: PCR and sequencing analysis of *NSD1*
  2nd tier: large deletion/duplication analysis (MLPA) of *NSD1*

Williams-Beuren syndrome

OMIM: 194050, 609757

- Gene: *WBSCR*-gene region, locus 7q11.2
- Indication: cardiovascular disease (supravalvular aortic stenosis (SVAS), elastin arteriopathy, peripheral pulmonary stenosis, hypertension), distinctive facies, mental retardation (usually mild), a specific cognitive profile, unique personality characteristics, growth abnormalities and endocrine abnormalities (hypercalcemia, hypercalciuria, hypothyroidism and early puberty).
- TAT: approx. 2 weeks
- Method: large deletion/duplication analysis (MLPA) of *WBSCR*-gene region

Connective Tissue Disorders

Ehlers-Danlos syndrome type I+II (classical type)

OMIM: 130000, 130010

- Genes: *COL5A1, COL5A2*, loci 9q34, 2q31
- Inheritance: autosomal dominant
- Indication: joint hypermobility, hyperextensible skin, atrophic and "cigarette paper" scars
- TAT: approx. 3-4 weeks
- Method:
  1st tier: PCR and sequencing analysis of *COL5A1* and *COL5A2*
  2nd tier: large deletion/duplication analysis (MLPA) of *COL5A1*

Ehlers-Danlos syndrome type IV (vascular type)

OMIM: 130050

- Gene: *COL3A1*, locus 2q31
- Inheritance: autosomal dominant
- Indication: skin hyperextensibility, atrophic scarring, easy bruising, thin and translucent skin, joint hypermobility, rupture of inner organs and arteries, facial appearance: hollow cheeks, prominent staring eyes, pinched nose, lobeless ears
- TAT: approx. 3-4 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *COL3A1*
  2nd tier: large deletion/duplication analysis (MLPA) of *COL3A1*

Ehlers-Danlos syndrome type VI (Kyphoscoliosis)

OMIM: 225400

- Gene: *PLOD1*, locus 1p36
- Inheritance: autosomal recessive
- Indication: generalized joint laxity, progressive scoliosis, scleral fragility and globe rupture, muscle hypotonia at birth, tissue fragility.
- TAT: approx. 3-4 weeks
- Methods:
  1st tier: large deletion/duplication analysis (MLPA) of *PLOD1*
  2nd tier: PCR and sequencing analysis of *PLOD1*

Ehlers-Danlos syndrome type VIIA+B (Arthrochalasia)

OMIM: 130060

- Genes: *COL1A1, COL1A2*, loci 17q32.32, 7q22.1
- Inheritance: autosomal dominant
- Indication: severe generalized joint hypermobility, recurrent subluxations, congenital hip dislocation, skin hyperextensibility, atrophic scars
- TAT: approx. 3-4 weeks
- Method: PCR and sequencing analysis of the most common mutations in *COL1A1* and *COL1A2* leading to EDS VIIA+B

Loeys-Dietz syndrome

OMIM: 609192, 610168

- Genes: *TGFBR1, TGFBR2*, loci 9q22, 3p22
- Inheritance: autosomal dominant
- Indication: typical facial dysmorphic features (hypertelorism, cleft palate/bifid uvula, craniosynostosis), aggressive arterial/aortic aneurysm, arterial tortuosity, Marfan syndrome like appearance
- TAT: approx. 2 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *TGFBR1* and *TGFBR2*
  2nd tier: large deletion/duplication analysis (MLPA) of *TGFBR2*

Marfan syndrome

OMIM: 154700

- Gene: Fibrillin-1-gene (*FBN1*), locus 15q21.1
- Inheritance: autosomal dominant
- Indication: connective tissue weakness, bone overgrowth with disproportionately long extremities and joint laxity, aortic root dilatation, aortic aneurysm, myopia, ectopia lentis
- TAT: approx. 3-4 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *FBN1*
  2nd tier: large deletion/duplication analysis (MLPA) of *FBN1*

Osteogenesis Imperfecta

OMIM: 166200, 166210

- Genes: *COL1A1, COL1A2*, loci 17q32.32, 7q22.1
- Inheritance: autosomal dominant
- Indication: increased bone fragility with variable severity, blue sclera, dentinogenesis imperfect, hearing impairment
- TAT: approx. 3-4 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *COL1A1* and *COL1A2*
  2nd tier: large deletion/duplication analysis (MLPA) of *COL1A1* and *COL1A2*

Endocrinology

Congenital adrenal hyperplasia, CAH, 21-Hydroxylase deficiency

OMIM: 201910
- Gene: *CYP21A2*, locus 6p21.3
- Inheritance: autosomal recessive
- Indication: Congenital adrenal hyperplasia, salt wasting, precocious puberty or adrenarche, virilization, hirsutism
- TAT: approx. 2 weeks, prenatal analysis: approx. 7 days
- Methods: large deletion/duplication analysis (MLPA) and PCR and sequencing analysis of *CYP21A2*

Hyperinsulinism

Severe neonatal type

OMIM: 600509, OMIM: 600937
- Gene: *ABCC8* (=*SUR1*), *Kir6.2* (=*KCNJ11*), loci 11p15.1, 11p15.1
- Inheritance: autosomal recessive
- Indication: persistent hypoglycemia in the first years of life, severe refractory hypoglycemia in the first 48 hours of life
- TAT: approx. 2-3 weeks
- Methods:
  1st tier: PCR and sequencing analysis of A*BCC8*
  2nd tier: large deletion/duplication analysis (MLPA) of *ABCC8*
  3rd tier: PCR and sequencing analysis of *Kir6.2*

Mild type

OMIM: 138130, 138079
- Inheritance: autosomal dominant
- Gene: *GLUD1*, *GCK,* loci 10q23.3, 7p15-p13
- Indication: persistent hypoglycemia in the first years of life, Hyperinsulinism–hyperammonaemia (HI/HA) syndrome, nonspecific symptoms including seizures, hypotonia, poor feeding and apnea
- TAT: approx. 3 weeks
- Methods: Detection of point mutations and large deletions/duplications

1st tier: PCR and sequencing analysis of exons 6- 8, 11 and 12 of *GLUD1*
2nd tier: PCR and sequencing analysis of exons 1-5, 9, 10 and 13 of *GLUD1*
3rd tier: PCR and sequencing analysis of *GCK*

Hyperproinsulinemia

OMIM: 613370
- Gene: *INS,* locus 11p15.5
- Inheritance: autosomal dominant
- Indication: circulating proinsulin, apparent insulin resistance with hyperglycemia and hyperinsulinemia but good response to insulin treatment
- TAT: approx. 1 week
- Method: PCR and sequencing analysis of *INS*

Kallmann syndrome

OMIM: 308700, 147950
- Gene: *KAL1, FGFR1,* loci Xp22.3, 8p11.2-p11.1
- Inheritance: X-linked recessive (*KAL1*), autosomal dominant (*FGFR1*)
- Indication: idiopathic or isolated hypogonadotropic hypogonadism (IHH) and anosmia or hyposmia
- TAT: approx. 2-3 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *KAL1* and *FGFR1*
  2nd tier: large deletion/duplication analysis (MLPA) of *KAL1* and *FGFR1*

MODY (Maturity-Onset Diabetes of the Young)

OMIM: 606391

MODY1

OMIM: 125850
- Gene: *HNF4A*, locus 20q12-q13.1
- Inheritance: autosomal dominant
- Indication: positive family history of Diabetes mellitus, early manifestation (before the age of 25), manifestation at first with mild symptoms, no beta cell autoimmunity

- TAT: approx. 2 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *HNF4A*
  2nd tier: large deletion/duplication analysis (MLPA) of *HNF4A, GCK, HNF1A, HNF1B*

MODY2

OMIM: 125851
- Gene: *GCK,* locus 7p15-p13
- Inheritance: autosomal dominant
- Indication: positive family history of Diabetes mellitus, early manifestation (before the age of 25), manifestation at first with mild symptoms, no beta cell autoimmunity, gestational diabetes
- TAT: approx. 2 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *GCK*
  2nd tier: large deletion/duplication analysis (MLPA) of *HNF4A, GCK, HNF1A, HNF1B*

MODY3

OMIM: 600496
- Gene: *HNF1A* (=*TCF1*), locus 12q24.2
- Inheritance: autosomal dominant
- Indication: positive family history of Diabetes mellitus, early manifestation (before the age of 25), manifestation at first with mild symptoms, no beta cell autoimmunity, gestational diabetes
- TAT: approx. 2 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *HNF1A*
  2nd tier: large deletion/duplication analysis (MLPA) of *HNF4A, GCK, HNF1A, HNF1B*

MODY4

OMIM: 606392
- Gene: *PDX1* (=*IPF1*), locus 13q12.2
- Inheritance: autosomal dominant

- Indication: positive family history of Diabetes mellitus, early manifestation (before the age of 25), manifestation at first with mild symptoms, no beta cell autoimmunity, pancreatic abnormalities
- TAT: approx. 1 week
- Method: PCR and sequencing analysis of *PDX1* (=*IPF1*)

MODY5 (Renal Cysts and Diabetes syndrome, RCAD)

OMIM: 137920
- Gene: *HNF1B* (=*TCF2*), locus 17q12
- Inheritance: autosomal dominant
- Indication: positive family history of Diabetes mellitus, early manifestation (before the age of 25), manifestation at first with mild symptoms, no beta cell autoimmunity, non-diabetic renal disease, genital malformations and liver dysfunction
- TAT: approx. 2 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *HNF1B*
  2nd tier: large deletion/duplication analysis (MLPA) of *HNF4A, GCK, HNF1A, HNF1B*

MODY6

OMIM: 606394
- Gene: *NEUROD1*, locus 2q31
- Inheritance: autosomal dominant
- Indication: positive family history of Diabetes mellitus, early manifestation (before the age of 25), manifestation at first with mild symptoms, no beta cell autoimmunity
- TAT: approx. 1 week
- Method: PCR and sequencing analysis of *NEUROD1*

MODY 7

OMIM: 610508
- Gene: *KLF11*, locus 2p25.11
- inheritance: autosomal dominant

- Indication: positive family history of Diabetes mellitus, early manifestation (before the age of 25), manifestation at first with mild symptoms, no beta cell autoimmunity
- TAT: approx. 1 week
- Method: PCR and sequencing analysis of *KLF11*

MODY 10

OMIM: 610508
- Gen: *INS*, Locus 11p15.5
- inheritance: autosomal dominant
- Indication: hyperproinsulinemia, positive family history of Diabetes mellitus, early manifestation (before the age of 25), manifestation at first with mild symptoms, no beta cell autoimmunity
- TAT: approx. 1 week
- Method: PCR and sequencing analysis of *INS*

Neonatal Diabetes

Permanent/transient neonatal Diabetes

OMIM: 600509, OMIM: 600937
- Genes: *ABCC8* (=*SUR1*), loci 11p15.1, *Kir6.2* (=*KCNJ11*), Locus 11p15.1,
- inheritance: autosomal dominant for *KCNJ11*, autosomal dominant or autosomal recessive for *ABCC8* und *INS,* autosomal recessive for *GCK*
- Indication: Hyperglycemiain the first 6 months of life, intrauterine growth retardation , low birth weight, failure to thrive, deficiency of subcutaneous adipose tissue, low C-peptide levels
- TAT: approx. 3-4 weeks
- Methods:
  1st tier: PCR and sequencing analysis of Kir6.2 (=KCNJ11)
  2nd tier: PCR and sequencing analysis of ABCC8
  3rd tier: PCR and sequencing analysis of INS
  4th tier: uniparental disomy 6 (UPD6 analysis) (parents' sample required)
  5th tier: PCR and sequencing analysis of GCK

Obesity (early onset, MC4-receptor deficiency)

OMIM: 601665
- Gene: *MC4R*, locus 18q21.32

- inheritance: autosomal dominant
- Indication: severe and early onset obesity increased lean mass, increased linear growth, hyperphagia, and severe hyperinsulinemia
- TAT: approx.1- 2 weeks
- Methods:
  1st tier PCR and sequencing analysis of *MC4R*
  2nd tier: : large deletion/duplication analysis (MLPA) of *MC4R*

Eye diseases

Age related macular degeneration (AMD)

OMIM: 610698

- Gene: *CFH*, locus 1q32
- Indication: assessment of the risk for age-related macular degeneration
- TAT: approx. 1 week
- Method: PCR, sequencing analysis; detection of the polymorphism p.Tyr402His

Leber's hereditary optic neuropathy (LHON)

OMIM: 535000

- Genes: *ND1, ND4, ND6*, mitochondrial genome
- Indication: bilateral, painless, subacute visual failure that develops during young adult life, unilateral or bilateral optic neuropathy, centrocecal scotoma
- TAT: approx. 1 week
- Method: PCR and sequencing analysis of the common mutations m.11778G>A, m.3460G>A, m.14484T>A

Optic Atrophy 1 (OPA1)

OMIM: 165500

- Gene: *OPA1*, locus 3q28-q29
- Indication: bilateral neuropathy of the optic nerve, scotoma
- TAT: approx. 2-3 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *OPA1*
  2nd tier: large deletion/duplication analysis (MLPA) of *OPA1*

Hereditary cancer syndromes

OMIM: 175100, 608456, 604933

Familial adenomatous polyposis (FAP)

OMIM: 611731

- Genes: *APC*, *MUTYH*, locus 5q21-q22, 1p34.3-p32.1
- Indication: suspected classic or attenuated FAP, flat adenoma syndrome, suspected Gardner or Turcot syndrome, suspected classic FAP with extracolonic manifestations
- TAT: approx. 4 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *APC*
  2nd tier: large deletion/duplication analysis (MLPA) of *APC*
  3rd tier:PCR and sequencing analysis of exon 7 and 13 of *MUTYH* for the two most common mutations
  4th tier: PCR and sequencing analysis of the exons 1-6, 8-12,14-16 of *MUTYH*

Hereditary non-polyposis colorectal cancer (HNPCC)

OMIM: 114500

- Genes: *MSH2, MLH1*, *MSH6*, loci 2p21-22, 3p21, 2p16
- Indication: positive family history for colon cancer or HNPCC-associated tumors, patient fulfils the updated Bethesda Guidelines (2004) or the classic Amsterdam Criteria
- TAT: approx. 2-3 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *MLH1*
  2nd tier: PCR and sequencing analysis of *MSH2*
  3rd tier: large deletion/duplication analysis (MLPA) of *MSH2, MLH1*
  4th tier: PCR and sequencing analysis of *MSH6*
  5th tier: large deletion/duplication analysis (MLPA) of *MSH6*

Hereditary Breast/Ovarian cancer

OMIM: 113705, 600185

- Genes: *BRCA1*, locus 17q21, *BRCA2*, locus 13q12.3, *CHEK2*, locus22q12
- Indication: suspected hereditary breast-ovarian carcinoma, positive family history for breast-ovarian cancer
- TAT: approx. 3-4 weeks

- Methods:
  1st tier: PCR and sequencing analysis of *BRCA1, BRCA2*
  2nd tier: large deletion/duplication analysis (MLPA) of *BRCA1, BRCA2*
  3rd tier: PCR and sequencing analysis of *CHEK2*, mutations c.1100delC, c.444+1G>A, c.470T>C)
  4th tier: large deletion/duplication analysis (MLPA) of *CHEK2*

Multiple endocrine neoplasia type 1, MENI

OMIM: 131100

- Gene: *MEN1*, locus 11q13.1
- Indication: tumors of parathyroids, pancreatic islets, duodenal endocrine cells and the anterior pituitary
- TAT: approx. 2 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *MEN1*
  2nd tier: large deletion/duplication analysis (MLPA) of *MEN1*

Multiple endocrine neoplasia type 2, MENII

OMIM: 171400

- Gene: *RET*, locus 10q11.2
- Indication: isolated medullary carcinoma of the thyroid (MTC, C-Cell carcinoma), pheochromocytoma, hyperparathyroidism, positive family history for MEN2
- TAT: approx. 2 weeks
- Methods:
  1st tier: PCR and sequencing analysis of exons 10-11, 13-16 of *MEN2*
  2nd tier: PCR and sequencing analysis of exons 1-9, 12, 17-20 of *MEN2*
  3rd tier: large deletion/duplication analysis (MLPA) of *MEN2*

Neurofibromatosis type 1, NF1

OMIM: 162200

- Gene: *NF1*, locus 17q11.2
- Indication: multiple café au lait spots (>5 mm), axillary and inguinal freckling, multiple discrete dermal neurofibromas, iris Lisch nodules
- TAT: approx. 3-4 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *NF1*
  2nd tier: large deletion/duplication analysis (MLPA) of *NF1*

Risk for Prostate cancer (5-α-Reductase)

OMIM: 607306

- Gene and location: *SRD5A2*-Gene, Locus 2p23
- Indication: assessment of the risk for prostate cancer
- TAT: approx. 1 week
- Method: PCR, sequencing analysis; detection of the polymorphisms p.Ala49Thr, p.Val89Leu

Von-Hippel-Lindau syndrome, VHL

OMIM: 193300

- Gene: *VHL*, locus 3p25.3
- Indication: retinal angioma, cerebellar or spinal cord hemangioblastoma, renal cell carcinoma, pheochromocytoma
- TAT: approx. 1-2 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *VHL*
  2nd tier: large deletion/duplication analysis (MLPA) of *VHL*

Infertility

Female

Factor V

OMIM: 227400

- Gene and location: *F5*, Locus 1q23
- Methods:
  Real-time-PCR (LightCycler technique), genotyping of the polymorphism p.Arg506Gln in the F5-gene (Leiden mutation)
  PCR-RFLP, genotyping of the polymorphism p.His1299Arg in the *F5*-gene

Mannose binding lectin (MBL)

OMIM: 614372

- Gene: *MBL2*, locus 10q21.1
- Indication: recurrent preterm births due to chorioamnionits
- Methods: : Real-Time-PCR (Light-Cycler-technique): detection of the variants p.Gly54Asp, p.Gly57Glu und p.Arg52Cys

Methylenetetrahydrofolate reductase, MTHFR

OMIM: 236250

- Gene: *MTHFR*, locus 1p36.3
- Method: Real-time-PCR (LightCycler technique), genotyping of the mutations c.665C>T (legacy: c.677C>T) (p.Ala222Val) and c.1286A>C (legacy c.1298A>C) (p.Glu429Ala) in the *MTHFR*-gene

Plasminogen-Activator-Inhibitor type 1, PAI1

OMIM: 173360

- Gene: *PAI1*, locus 7q21.3-22
- Method: Real-time-PCR (LightCycler technique), genotyping of the polymorphism 4G/5G (c.-675delG) in the *PAI1*-gene

Prothrombin / Factor II

OMIM: 176930

- Gene: *F2*, locus 11q11
- Method: Real-time-PCR (LightCycler technique) genotyping of the polymorphism g.20210G>A in the 3´UTR of the *F2*-gene

Male

Azoospermia factor (AZF)

OMIM: 415000

- AZF-locus Yq11
- Indication: Infertility due to none-obstructive azoospermia, oligozoospermia
- TAT: approx. 1-2 weeks
- Method: PCR; detection of microdeletions in the AZF region

Congenital bilateral aplasia of the vas deferens, CBAVD

OMIM: 277180

- Gene: *CFTR*, locus 7q31.3
- Indication: Infertility due to obstructive azoospermia
- TAT: 1-3 weeks; depending on the analysis performed
- Methods:
  - common mutation panel: PCR, reverse hybridization to detect 36 common mutations
  - sequencing analysis of the *CFTR*, large deletion/duplication analysis (MLPA) of *CFTR*

Inner Organs
Intestine

Inflammatory bowel (Crohn) disease

OMIM: 266600
- Genet: *NOD2*, locus 16q12.1
- inheritance: autosomal dominant
- Indication: relapsing intestinal inflammation
- TAT: approx.1 week
- Methods: Real-time PCR (LightCycler technique) detection of the mutations p.Arg702Trp, p.Gly908Arg, p.Leu1007Profs*2

Kidney
Adult dominant polycystic kidney disease, ADPKD

OMIM: 613095, 173900
- Genes: *PKD1, PKD2*, loci 16p13.3, 4q21-23
- Inheritance: autosomal dominant
- Indication: renal and liver cysts, with further complication of hypertension
- TAT: approx. 4 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *PKD1, PKD2*
  2nd tier: large deletion/duplication analysis (MLPA) of *PKD1, PKD2*

Alport syndrome

OMIM: 303630, 203780, 104200
- Genes: *COL4A5*, locus Xq22.3; COL4A4, locus 2q36.3, *COL4A3*, locus 2q36.3
- inheritance: X-chromosomal (*COL4A5*), autosomal dominant/recessive (*COL4A4, COL4A3*)
- Indication: micro- or macrohematuria, proteinuria with progression to end stage renal disease, focal thickening or splitting of the glomerular basement membrane, progressive bilateral sensorineural hearing loss, anterior lenticonus.

- TAT: approx. 4 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *COL4A5*
  2nd tier: PCR and sequencing analysis of *COL4A3*
  3rd tier: PCR and sequencing analysis of *COL4A4*
  4th tier: large deletion/duplication analysis (MLPA) of *COL4A5*

Liver

Crigler-Najjar syndrome type I/II

OMIM: 143500; 606785

- Gene: *UGT1A1*, locus 2q37
- Inheritance: autosomal recessive
- Indication: Hyperbilirubinemia, congenital familial nonhemolytic jaundice with kernicterus
- TAT: approx. 2 weeks
- Methods:
  1st tier: PCR and fragment analysis to detect the TA-expansion in the promoter of *UGT1A1*
  2nd tier: PCR and sequencing analysis of *UGT1A1*

Hemochromatosis type 1

OMIM: 235200

- Gene: *HFE*, locus 6p21.3
- Inheritance: autosomal recessive
- Indication: increased serum ferritin and transferrin saturation, in advanced disease stages liver fibrosis, cirrhosis, bronzed skin, diabetes
- TAT: 1. stage approx. 1 week, 2. stage approx. 2 weeks
- Method:
  1st tier: Real-time PCR (LightCycler technique), detection of the most common mutations p.Cys282Tyr, p.His63Asp and p.Ser65Cys
  2nd tier: PCR and sequencing analysis of *HFE*
  3rd tier : large deletion/duplication analysis (MLPA) of *HFE, SLC40A1, TFR2, HJV, HAMP*

Hemochromatosis type 2A and 2B (juvenile type)

OMIM: 602390

- Genes: *HAMP* (Hepcidin), *HJV* (Hemojuvelin), loci 19q13, 1q21.1
- Inheritance: autosomal recessive

- Indication: severe iron overload occurring typically in the first to third decade of life, adult hemochromatosis with additional heterozygous mutation p.Cys282Tyr in the *HFE*-gene; increase in skin pigmentation, diabetes mellitus, congestive heart failure and/or arrhythmias, arthritis
- TAT: approx. 2 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *HAMP* and *HJV,*
  2nd tier: large deletion/duplication analysis (MLPA) of *HFE, SLC40A1, TFR2, HJV, HAMP*

Hemochromatosis type 3

OMIM: 604250

- Gene: *TFR2,* locus 7q22.1
- Inheritance: autosomal recessive
- Indication: severe increased serum ferritin and transferrin saturation, in advanced disease stages liver fibrosis, cirrhosis
- TAT: approx. 2 weeks
- Methods:
  1st tier PCR and, sequencing analysis of *TFR2*
  2nd tier: large deletion/duplication analysis (MLPA) of *HFE, SLC40A1, TFR2, HJV, HAMP*

Hemochromatosis type 4

OMIM: 606069

- Gene: *SLC40A1,* locus 2q32.2
- Inheritance: autosomal dominant
- Indication: severe increased serum ferritin and transferrin saturation, in advanced disease stages liver fibrosis, cirrhosis
- TAT: approx. 2 weeks
- Methods:
  1st tier: PCR and, sequencing analysis of *SLC40A1*
  2nd tier: large deletion/duplication analysis (MLPA) of *HFE, SLC40A1, TFR2, HJV, HAMP*

Hyperbilirubinemia, Gilbert syndrome

OMIM: 143500

- Gene: *UGT1A1*, locus 2q37
- Inheritance: autosomal recessive

- Indication: Hyperbilirubinemia, congenital familial nonhemolytic jaundice with kernicterus
- TAT: approx. 2 weeks
- Method: PCR and fragment analysis, detection of the TA-repeat-expansion in the promoter of *UGT1A1*

Wilson disease

OMIM: 277900

- Gene: *ATP7B*, locus 13q14.3
- Inheritance: autosomal recessive
- Indication: Hepato-, splenomegaly, movement disorders (tremors, poor coordination, loss of fine-motor control, chorea, choreoathetosis) or rigid dystonia (mask-like facies, rigidity, gait disturbance, pseudobulbar involvement), Kayser-Fleischer ring
- TAT: approx. 1 week
- Methods:
  1st tier: Real-time-PCR (LightCycler technique), detection of the most common mutation p.His1069Gln)
  2nd tier: PCR and, sequencing analysis of *ATP7B*
  3rd tier: large deletion/duplication analysis (MLPA) of *ATP7B*

Lung

Alpha1-Antitrypsin Deficiency

OMIM: 107400

- Gene: *SERPINA1*, locus 14q32.1
- Inheritance: autosomal recessive
- Indication: chronic obstructive pulmonary disease (COPD) in adults, liver disease in children and adults, emphysema, Ikterus prolongatus, liver disease in adults, manifest as cirrhosis and fibrosis
- TAT: 1st tier: approx. 1 week, 2nd tier: 1-2 weeks
- Methods:
  1st tier: Real-time-PCR (LightCycler technique) for detection of the most common mutation PiS* and PiZ*
  2nd tier: PCR and sequencing analysis of *SERPINA1*

Cystic Fibrosis Transmembrane Conductance Regulator, CFTR

OMIM: 219700

- Gene: *CFTR*, locus 7q31.2
- Inheritance: autosomal recessive
- Indication: obstructive lung disease, bronchiectasis, exocrine pancreas insufficiency, elevated sweat chloride concentration, meconium ileus
- TAT: approx. 1-3 weeks; depending on the analysis performed
- Methods:
  - p.Phe508del: Real-time-PCR (LightCycler technique) detection of the most common mutation p.Phe508del
  - common mutation panel: PCR, reverse hybridization to detect 36 common mutations
  - sequencing analysis of the *CFTR*, large deletion/duplication analysis (MLPA) of *CFTR*

Pancreas

Pancreatitis, hereditary
Genes: *PRSS1, SPINK1* and *CFTR*

OMIM: 167800

Indication: recurrent episodes of pancreatic attacks, which can progress to chronic pancreatitis, abdominal pain, nausea and vomiting, elevated amylase and lipase serum concentrations in children, onset of attacks typically occurs between within the first two decades of life, but can begin at any age

Cationic trypsinogen, PRSS1

OMIM: 276000

- Gene: *PRSS1* (Cationic trypsinogen), locus 7q35
- Inheritance: autosomal dominant, incomplete penetrance
- TAT: approx. 1 week
- Method: PCR, sequencing analysis of exons 2 and 3 of *PRSS1*

Serine Protease Inhibitor, Kazal type 1, SPINK1

OMIM: 167790

- Gene: *SPINK1* (Serine Protease Inhibitor, Kazal type 1), locus 5q32
- Inheritance: autosomal recessive, incomplete penetrance
- TAT: approx. 1 week
- Method: PCR and sequencing analysis of *SPINK1*

Cystic Fibrosis Transmembrane Conductance Regulator, CFTR

OMIM: 602421

- Gene: *CFTR*, locus 7q31.2
- Inheritance: autosomal recessive
- Indication: obstructive lung disease, bronchiectasis, exocrine pancreas insufficiency, elevated sweat chloride concentration, meconium ileus
- TAT: approx. 1-3 weeks; depending on the analysis performed
- Methods:
  - p.Phe508del: Real-time-PCR (LightCycler technique) to detect the most common mutation p.Phe508del
  - common mutation panel: PCR, reverse hybridization to detect 36 common mutations
  - sequencing analysis of the *CFTR*, large deletion/duplication analysis (MLPA) of *CFTR*

Intersexuality

Congenital adrenal hyperplasia, CAH, 21-Hydroxylase deficiency

OMIM: 201910

- Gene: *CYP21A2*, locus 6p21.3
- Inheritance: autosomal recessive
- Indication: Congenital adrenal hyperplasia, salt wasting, precocious puberty or adrenarche, virilization, hirsutism
- TAT: approx. 2 weeks, prenatal analysis: approx. 7 days
- Methods: large deletion/duplication analysis (MLPA) and PCR and sequencing analysis of *CYP21A2*

SRY

OMIM: 480000

- locus: Yp11.3
- Indication: primary amenorrhea, gonadal dysgenesis, suspected XX-males, suspected testicular feminization
- TAT: approx. 1 week
- Method: PCR

Metabolic disorders

Apolipoprotein A1

OMIM: 107680

- Gene: *APOA1*, locus 11q23
- Indication: early identification of at-risk patients for atherosclerosis, assessment of the risk for myocard infarcts and peripheral obstructive disease in patients with a positive family history
- TAT: approx. 1 week
- Method: PCR and sequencing analysis of *APOA1*

Apolipoprotein B

OMIM: 107730

- Gene: *APOB*, locus 2p24
- Indication: Dyslipoproteinemia, hypercholesteriolemia
- TAT: approx. 1 week
- Method: Real-time-PCR (LightCycler technique) detection of the most common mutations p.Arg3527Gln, p.Arg3527Trp, p.Arg3558Cys (legacy p.Arg3500Gln, p.Arg3500Trp, p.Arg3531Cys)

Apolipoprotein E

OMIM: 107741

- Gene: *APOE*, locus 19q13.2
- Indication: Dyslipoproteinemia, hypercholesterinemia, Alzheimer disease
- TAT: approx. 1 week
- Method: Real-time-PCR (LightCycler technique) for genotyping of *APOE*-alleles E2, E3, E4

Fabry disease, ·-Galactosidase-A deficiency

OMIM: 301500

- Gene: *GLA*, locus Xq22
- Inheritance: X-linked
- Indication: males with less than 1% α-galactosidase enzyme activity, periodic crises of severe pain in the extremities (acroparesthesias), appearance of vascular cutaneous lesions (angiokeratomas), hypohidrosis, characteristic corneal and lenticular opacities, and proteinuria, gradual deterioration of renal function to end-stage renal

disease (ESRD), most males successfully treated for ESRD develop cardiovascular and/or cerebrovascular disease
- TAT: approx. 2 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *GLA*
  2nd tier: large deletion/duplication analysis (MLPA) of *GLA*

Fructose intolerance, hereditary

OMIM: 229600
- Gene: Aldolase B (*ALDOB*), locus 9q22.3
- Inheritance: autosomal recessive
- Indication: nausea and abdominal pain after eating fruits and fructose/sucrose-containing foods, fructose-/ saccharose-intolerance; hypoglycemia, vomiting, nonspecific liver dysfunction
- TAT: 1st tier: approx. 1 week, 2nd tier: approx. 1-2 weeks
- Methods:
  1st tier: PCR and sequencing analysis of exons 5, 6 and 9 to detect the most common mutations of *ALDOB*
  2nd tier: PCR and sequencing analysis of exons 2- 4, 7, 8 of *ALDOB*, large deletion/duplication analysis (MLPA) of *ALDOB*

Glucose-6-Phosphate Dehydrogenase Deficiency

OMIM: 305900
- Gene: *G6PD*, locus Xq28
- Inheritance: X-linked recessive
- Indication: Anemia (nonspherocytic hemolytic anemia), hemolytic episodes, Favism
- TAT: approx. 2 weeks
- Method: PCR and sequencing analysis of *G6PD*

Hyperinsulinism

Severe neonatal type

OMIM: 600509, OMIM: 600937
- Gene: *ABCC8* (=*SUR1*), *Kir6.2* (=*KCNJ11*), loci 11p15.1, 11p15.1
- Inheritance: autosomal recessive
- Indication: persistent hypoglycemia in the first years of life, severe refractory hypoglycemia in the first 48 hours of life
- TAT: approx. 2-3 weeks

- Methods:
  1st tier: PCR and sequencing analysis of A*BCC8*
  2nd tier: large deletion/duplication analysis (MLPA) of *ABCC8*
  3rd tier: PCR and sequencing analysis of *Kir6.2*

Mild type

OMIM: 138130, 138079
- Inheritance: autosomal dominant
- Gene: *GLUD1*, *GCK,* loci 10q23.3, 7p15-p13
- Indication: persistent hypoglycemia in the first years of life, Hyperinsulinism–hyperammonaemia (HI/HA) syndrome, nonspecific symptoms including seizures, hypotonia, poor feeding and apnea
- TAT: approx. 3 weeks
- Methods: Detection of point mutations and large deletions/duplications
  1st tier: PCR and sequencing analysis of exons 6- 8, 11 and 12 of *GLUD1*
  2nd tier: PCR and sequencing analysis of exons 1-5, 9, 10 and 13 of *GLUD1*
  3rd tier: PCR and sequencing analysis of *GCK*

Hyperproinsulinemia

OMIM: 613370
- Gene: *INS,* locus 11p15.5
- Inheritance: autosomal dominant
- Indication: circulating proinsulin, apparent insulin resistance with hyperglycemia and hyperinsulinemia but good response to insulin treatment
- TAT: approx. 1 week
- Method: PCR and sequencing analysis of *INS*

Lactose intolerance

OMIM: 223100
- Gene: Lactase gene (*LCT*), locus 2q21
- Inheritance: autosomal recessive
- Indication: Lactose intolerance, abdominal symptoms, including stomach cramps, bloating and flatulence after intake of lactose-containing food
- TAT: approx. 1 week

- Method: Real-time-PCR (LightCycler technique); detection of the polymorphism -13910T>C in the promoter of the *LCT*-gene

LDL-receptor

OMIM: 143890

- Gene: *LDLR*, locus 19p13.2
- Inheritance: autosomal dominant
- Indication: Hypercholesterolemia, tendinous xanthomas, corneal arcus, and coronary artery disease
- TAT: approx. 2-3 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *LDLR*
  2nd tier: PCR large deletion/duplication analysis (MLPA) of *LDLR*

MCAD (Medium-Chain Acyl-CoA Dehydrogenase) Deficiency

OMIM: 201450

- Gene: *ACADM*, locus 1p31
- Inheritance: autosomal recessive
- Indication: positive acylcarnitine screening in newborn, hypoketotic hypoglycemia, vomiting, and lethargy triggered by a common illness, seizures, hepatomegaly and acute liver disease, onset typically between three and 24 months of age
- TAT: approx. 1 week
- Methods:
  1st tier: PCR and sequencing analysis of exons 3, 4, 11 to detect the most common mutations in *ACADM*
  2nd tier: PCR and sequencing analysis of exons 1, 2, 5-10, 12 of *ACADM*

MODY (Maturity-Onset Diabetes of the Young) OMIM: 606391

MODY1

OMIM: 125850

- Gene: *HNF4A*, locus 20q12-q13.1
- Inheritance: autosomal dominant

- Indication: positive family history of Diabetes mellitus, early manifestation (before the age of 25), manifestation at first with mild symptoms, no beta cell autoimmunity
- TAT: approx. 2 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *HNF4A*
  2nd tier: large deletion/duplication analysis (MLPA) of *HNF4A, GCK, HNF1A, HNF1B*

MODY2

OMIM: 125851
- Gene: *GCK,* locus 7p15-p13
- Inheritance: autosomal dominant
- Indication: positive family history of Diabetes mellitus, early manifestation (before the age of 25), manifestation at first with mild symptoms, no beta cell autoimmunity, gestational diabetes
- TAT: approx. 2 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *GCK*
  2nd tier: large deletion/duplication analysis (MLPA) of *HNF4A, GCK, HNF1A, HNF1B*

MODY3

OMIM: 600496
- Gene: *HNF1A* (= *TCF1*), locus 12q24.2
- Inheritance: autosomal dominant
- Indication: positive family history of Diabetes mellitus, early manifestation (before the age of 25), manifestation at first with mild symptoms, no beta cell autoimmunity, gestational diabetes
- TAT: approx. 2 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *HNF1A*
  2nd tier: large deletion/duplication analysis (MLPA) of *HNF4A, GCK, HNF1A, HNF1B*

MODY4

OMIM: 606392

- Gene: *PDX1* (=*IPF1*), locus 13q12.2
- Inheritance: autosomal dominant
- Indication: positive family history of Diabetes mellitus, early manifestation (before the age of 25), manifestation at first with mild symptoms, no beta cell autoimmunity, pancreatic abnormalities
- TAT: approx. 1 week
- Method: PCR and sequencing analysis of *PDX1* (=*IPF1*)

MODY5 (Renal Cysts and Diabetes syndrome, RCAD)

OMIM: 137920

- Gene: *HNF1B* (=*TCF2*), locus 17q12
- Inheritance: autosomal dominant
- Indication: positive family history of Diabetes mellitus, early manifestation (before the age of 25), manifestation at first with mild symptoms, no beta cell autoimmunity, non-diabetic renal disease, genital malformations, and liver dysfunction
- TAT: approx. 2 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *HNF1B*
  2nd tier: large deletion/duplication analysis (MLPA) of *HNF4A, GCK, HNF1A, HNF1B*

MODY6

OMIM: 606394

- Gene: *NEUROD1*, locus 2q31
- Inheritance: autosomal dominant
- Indication: positive family history of Diabetes mellitus, early manifestation (before the age of 25), manifestation at first with mild symptoms, no beta cell autoimmunity
- TAT: approx. 1 week
- Method: PCR and sequencing analysis of *NEUROD1*

MODY 7

OMIM: 610508
- Gene: *KLF11*, locus 2p25.11
- inheritance: autosomal dominant
- Indication: positive family history of Diabetes mellitus, early manifestation (before the age of 25), manifestation at first with mild symptoms, no beta cell autoimmunity
- TAT: approx. 1 week
- Method: PCR and sequencing analysis of *KLF11*

MODY 10

OMIM: 610508
- Gen: *INS*, Locus 11p15.5
- inheritance: autosomal dominant
- Indication: hyperproinsulinemia, positive family history of Diabetes mellitus, early manifestation (before the age of 25), manifestation at first with mild symptoms, no beta cell autoimmunity
- TAT: approx. 1 week
- Method: PCR and sequencing analysis of *INS*

Neonatal Diabetes

Permanent/transient neonatal Diabetes

OMIM: 600509, OMIM: 600937
- Genes: *ABCC8* (=*SUR1*), loci 11p15.1, *Kir6.2* (=*KCNJ11*), Locus 11p15.1,
- inheritance: autosomal dominant for *KCNJ11*, autosomal dominant or autosomal recessive for *ABCC8* und *INS,* autosomal recessive for *GCK*
- Indication: Hyperglycemiain the first 6 months of life, intrauterine growth retardation , low birth weight, failure to thrive, deficiency of subcutaneous adipose tissue, low C-peptide levels
- TAT: approx. 3-4 weeks

Methods:
1st tier: PCR and sequencing analysis of Kir6.2 (=KCNJ11)
2nd tier: PCR and sequencing analysis of ABCC8
3rd tier: PCR and sequencing analysis of INS
4th tier: uniparental disomy 6 (UPD6 analysis) (parents' sample required)
5th tier: PCR and sequencing analysis of GCK

Phenylketonuria / non-PKU mild hyperphenylalaninemia, PKU / HPA

OMIM: 261600

- Gene: Phenylalanin-hydroxylase (*PAH*), locus 11q22.3
- Inheritance: autosomal recessive
- Indication: positive phenylalanine screening in newborn: plasma phenylalanine concentrations higher than 800 µmol/L, hyperphenylalaninemia
- TAT: approx. 2 weeks
- Methods:
  1st tier: PCR and sequencing analysis of *PAH*
  2nd tier: large deletion/duplication analysis (MLPA) of *PAH*

Mitochondrial diseases

CPEO, Kearns-Sayre syndrome, Pearson syndrome, Mitochondrial DNA Deletion Syndromes

OMIM: 530000, 557000

- locus: mitochondrial genome
- Indication: suspected mitochondrial disease, pigmentary retinopathy, progressive external ophthalmoplegia (PEO), sideroblastic anemia and exocrine pancreas dysfunction, ptosis, paralysis of the extraocular muscles (ophthalmoplegia), and variably severe proximal limb weakness
- TAT: approx. 1 week
- Method: Long range PCR, detection of deletions / duplications of the mitochondrial genome

MELAS, Diabetes-Deafness syndrome

OMIM: 540000

- Gene: *MT-TL1*, mitochondrial genome
- Indication: generalized tonic-clonic seizures that are often associated with stroke-like episodes of transient hemiparesis or cortical blindness, atypical diabetes, deafness, recurrent headaches, cardiac failure, renal failure
- TAT: approx. 1 week
- Method: PCR-RFLP, quantification; detection of the mutation m.3243G>A

Leber's hereditary optic neuropathy (LHON)

OMIM: 535000

- Genes: *ND1, ND4, ND6*, mitochondrial genome
- Indication: bilateral, painless, subacute visual failure that develops during young adult life, unilateral or bilateral optic neuropathy, centrocecal scotoma
- TAT: approx. 1 week
- Method: PCR and sequencing analysis of the common mutations m.11778G>A, m.3460G>A, m.14484T>A

Leigh- /NARP syndrome

OMIM: 256000, 551500

- Gene: *MT-ATP6*, mitochondrial genome
- Indication: Decompensation (often with lactic acidosis) during an intercurrent illness typically associated with psychomotor retardation or regression, neurologic features include hypotonia, spasticity, movement disorders (including chorea), cerebellar ataxia, and peripheral neuropathy
- TAT: approx. 1 week
- Method: PCR-RFLP, quantification; detection of the mutations m.8993T>G and m.8993T>C

MERRF syndrome

OMIM: 545000

- Gene: *MT-TK*, mitochondrial genome
- Indication: myoclonus epilepsy („ragged-red fibers" in the muscle biopsy), generalized epilepsy, ataxia, weakness, dementia, hearing loss, short stature, optic atrophy, and cardiomyopathy with Wolff-Parkinson-White (WPW) syndrome
- TAT: approx. 1 week
- Method: PCR-RFLP, quantification; detection of the mutation m.8344A>G

Neurodegenerative diseases

Adult-onset dominant leukodystrophy (ADLD)

OMIM: 169500

- Gene: *LMNB1*, locus 5q23.2

- Inheritance: autosomal dominant
- Indication: onset in the fourth or fifth decade of life, early autonomic abnormalities, pyramidal and cerebellar dysfunction, in neuroimaging symmetric demyelination of the CNS, lack of astrogliosis
- TAT: approx. 1 week
- Method: large deletion/duplication analysis (MLPA) of *LMNB1*

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy)

OMIM: 125310

- Gene: *NOTCH3*, locus 19p13.2-p13.1
- Inheritance: autosomal dominant
- Indication: history of migraine headaches, onset of cerebrovascular disease progressing to dementia, diffuse white matter lesions and subcortical infarcts in neuroimaging
- TAT: 1st tier: approx. 1-2 weeks, 2nd – 3rd tier: approx. 3-4 weeks
- Method:
  1st tier: PCR and sequencing analysis of exons 3-6 and 11 to detect the most common mutations of *NOTCH3*
  2nd tier: PCR and sequencing analysis of exons 1-2, 7-10,12-33
  3rd tier: large deletion/duplication analysis (MLPA) of *NOTCH3*

Huntington disease

OMIM: 143100

- Gene: *HTT*, locus 4p16.3
- Inheritance: autosomal dominant
- Indication: hyperkinesia, choreatic movements, disturbance of speech, dementia
- TAT: approx. 1 week
- Method: PCR, fragment analysis: identification of the CAG-repeat length / CGG repeat length of the *HTT*-gene

Neuromuscular disorders /Neuropathies

Neuropathy, hereditary motor and sensory

Neuropathy IA (HMSN type IA) / Charcot-Marie-Tooth disease type 1A (CMT type IA)

OMIM: 118220, 601097

- Gene: *PMP22*, locus 17p11.2
- Inheritance: autosomal dominant
- Indication: demyelinating peripheral neuropathy characterized by distal muscle weakness and atrophy, sensory loss, and slow nerve conduction velocity, pes cavus foot deformity, bilateral foot drop, age of onset 5-25 years
- TAT: approx.1 week
- Method:
  1st tier: large deletion/duplication analysis (MLPA) of *PMP22*
  2nd tier: PCR and sequencing analysis of *PMP22*

Neuropathy, hereditary with liability to pressure palsies (HNPP)

OMIM: 162500

- Gene: *PMP22*, locus 17p11.2
- Inheritance: autosomal dominant
- Indication: repeated focal pressure neuropathies such as carpal tunnel syndrome, peroneal palsy with foot drop, age of onset usually in the second or third decade of life
- TAT: approx.1 week
- Method:
  1st tier: large deletion/duplication analysis (MLPA) of *PMP22*
  2nd tier: PCR and sequencing analysis of *PMP22*

Muscular dystrophy Duchenne/Becker

OMIM: 310200, 300376

- Gene: Dystrophin (*DMD*), locus Xp21
- Inheritance: X-linked recessive
- Indication: increase in serum concentration of creatine phosphokinase (CK), muscular dystrophy, proximal weakness, cardiomyopathy
- TAT: approx. 1-2 weeks
- Method: large deletion/duplication analysis (MLPA) of *DMD*

Myotonic dystrophy type 1

OMIM: 160900

- Gene: *DMPK*, locus 19q13.2-q13.3
- Inheritance: autosomal dominant

- Indication: muscle weakness and wasting, myotonia, muscular dystrophy, cataract, hypogonadism and often cardiac conduction abnormalities
- TAT: approx. 2-3 weeks
- Methods:
  1st tier: PCR and fragment analysis
  2nd tier: Southern blot; identification of the CTG-repeat length

Myotonic dystrophy type 2 / proximal myotonic myopathy (PROMM)

OMIM: 602668

- Gene: *CNBP*, locus 3q21
- Inheritance: autosomal dominant
- Indication: myotonia and muscle dysfunction, muscular dystrophy, cataract, onset usually in the third decade of life
- TAT: approx. 2-3 weeks
- Methods:
  1st tier: PCR and fragment analysis
  2nd tier: Southern blot; identification of the CCTG-repeat length

Spinal muscular atrophy type I/II/III

OMIM: 253300, 253550, 253400

- Gene: *SMN1*, locus 5q12.2-q13.3
- Inheritance: autosomal recessive
- Indication: suspected Werdnig-Hoffmann or Kugelberg-Welander disease, severe proximal progressive muscle weakness, hypotonia, psychomotor delay, joint laxity, onset ranging from before birth to adolescence or young adulthood.
- TAT: approx.1 week
- Method: large deletion/duplication analysis (MLPA) of *SMN1* and *SMN2*

Spinal and Bulbar Muscular Atrophy,SBMA, Kennedy disease

OMIM: 313200

- Gene: *AR*, locus Xq11-q12
- Inheritance: X-linked recessive
- Indication: proximal muscle weakness, muscle atrophy, and fasciculations, gynecomastia, testicular atrophy, and reduced fertility as a result of mild androgen insensitivity, SBMA occurs only in males

- TAT: approx. 1 week
- Method: PCR, fragment analysis; identification of the CAG-repeat length

Osteoporosis

OMIM: 166710

Collagen1A1-gene (*COL1A1*)

OMIM: 120150

- Gene: *COL1A1*, locus 17q21.31-q22
- Indication: Osteoporosis, genotyping before starting a hormone substitution therapy to assess the risk for osteoporosis
- TAT: approx. 1 week
- Method: PCR-RFLP; genotyping of the Sp1 polymorphism in the *COL1A1*-gene

Vitamin D-receptor

OMIM: 601769

- Gene: *VDR*, locus 12q12-q14
- Indication: Osteoporosis, genotyping before starting a hormone substitution therapy to assess the risk for osteoporosis
- TAT: approx. 1 week
- Method: PCR-RFLP; genotyping of the BsmI polymorphism in the VDR-gene

Periodic fever

CINCA/NOMID, chronic neurologic cutaneous and articular syndrome / neonatal onset multisystemic inflammatory disease

OMIM: 607115

- Gene: *NLRP3*, locus 1q44
- Inheritance: autosomal dominant
- Indication: severe chronic inflammatory disease of early onset, cutaneous symptoms, central nervous system involvement and arthropathy
- TAT: approx. 2-3 weeks

- Methods:
  1st tier: PCR and sequencing analysis of exon 3 to detect the most common mutations of *NLRP3*
  2nd tier: PCR and sequencing analysis of exons 2, 4-9 of *NLRP3*

Familial mediterranean fever, FMF

OMIM: 249100

- Gene: Pyrin *MEFV*, locus 16p13
- Inheritance: autosomal recessive
- Indication: recurrent short episodes of inflammation and serositis including fever, peritonitis, synovitis, pleuritis, and, rarely, pericarditis and meningitis, amyloidosis
- TAT: 1st tier approx. 1-2 week, 2nd and 3rd tier appr. 2 weeks
- Methods:
  1st tier: PCR and sequencing analysis of the exons 1-3, 5 and 10 of
  2nd tier: PCR and sequencing analysis of the exons 4, 6-9
  3rd tier: large deletion/duplication analysis (MLPA) of *MEFV*

FCAS, familial cold autoinflammatory syndrome 1

OMIM: 120100

- Gene: *NLRP3*, locus 1q44
- Inheritance: autosomal dominant
- Indication: cold urticaria, recurrent attacks of a maculopapular rash associated with arthralgias, myalgias, fever and chills, and swelling of the extremities after exposure to cold
- TAT: approx. 2-3 weeks
- Methods:
  1st tier: PCR and sequencing analysis of exon 3 to detect the most common mutations of *NLRP3*
  2nd tier: PCR and sequencing analysis of exons 2, 4-9 of *NLRP3*

HIDS, Hyper-IgD syndrome

OMIM: 260920

- Gene: *MVK*, locus 12q24
- Inheritance: autosomal recessive
- Indication: recurrent febrile attacks with no fixed periodicity, accompanied by abdominal pain and arthralgia, increased IgD levels (>100 IU/ml)
- TAT: appr. 2 weeks
- Method: PCR, sequencing analysis of *MVK*

Muckle-Wells syndrome

OMIM: 191900

- Gene: *NLRP3*, locus 1q44
- Inheritance: autosomal dominant
- Indication: episodic skin rash, arthralgias, and fever associated with late-onset sensorineural deafness and renal amyloidosis
- TAT: approx. 2-3 weeks
- Methods:
  1st tier: PCR and sequencing analysis of exon 3 to detect the most common mutations of *NLRP3*
  2nd tier: PCR and sequencing analysis of exons 2, 4-9 of *NLRP3*

Tumor necrosis factor receptor-associated periodic syndrome, TRAPS; familial Hibernian fever

OMIM: 142680

- Gene: Tumor necrosis factor receptor- 1 (*TNFRSF1A*), locus 12p13.2
- Inheritance: autosomal dominant
- Indication: episodes of autoinflammation usually associated with fever, abdominal pain, myalgia, exanthema, arthralgia/arthritis and ocular involvement
- TAT: 2-3 weeks
- Methods:
  1st tier: PCR, sequencing analysis of the exons 2-4, 6, 7 and 10
  2nd tier: PCR, sequencing analysis of the exons 1, 5, 8 and 9

Pharmacogenetics

5- Flurouracil (5FU)- toxicity

OMIM: 274270

- Gene: *DPYD*, locus 1p22
- Inheritance: autosomal dominant
- Indication: risk assessing for toxicity for cancer patients for whom 5-fluorouracil-based chemotherapy is planned
- TAT: approx. 2-3 days
- Method: Real-time-PCR (LightCycler technique to detect the exon 14 skipping mutation (IVS14+1G>A) in the *DPYD*-gene

Glutathion-S-Transferase M1/T1

OMIM: 138350, 600436

- Gene: *GSTM1, GSTT1*, loci 1p13.3; 22q11.2
- Indication: chemical related hypersensitivity, assessing the risk of lung cancer
- TAT: approx. 1 week
- Method: PCR; detection of homozygous deletion of the *GSTM1*- and/or *GSTT1*-gene

N-Acetyltransferase

OMIM: 243400

- Gene: *NAT2*, locus 8p23.1-p21.3
- Indication: altered therapeutic response and toxicity to certain xenobiotics, identification of the patients acetylation status (slow – ultra rapid metabolizer)
- TAT: approx. 2 weeks
- Method: PCR, sequencing analysis of *NAT2*

Thiopurin S-Methyltransferase

OMIM: 187680

- Gene: *TPMT*, locus 6p22.3
- Indication: risk assessing for toxicity for cancer patients for whom azathioprine, 6-mercaptopurine and 6-thioguanine based chemotherapy is planned
- TAT: approx. 1 week
- Method: Real-time-PCR (LightCycler technique; detection of the polymorphisms c.238G>C, c.460G>A und c.719A>G)

UDP-Glucuronosyl-Transferase

OMIM: 191740

- Gene: *UGT1A1*, locus 2q37 (see also Hyperbilirubinemia)
- Indication: risk assessing for toxicity for cancer patients for whom Irinotecan based chemotherapy is planned
- TAT: approx. 2 weeks
- Methods:
  1st tier: PCR and fragment analysis to detect the TA-expansion in the promoter of *UGT1A1*
  2nd tier: PCR and sequencing analysis of *UGT1A1*

Thrombophilia / Atherosclerosis

OMIM: 188050
Genes: Factor V, Factor II (Prothrombin), *MTHFR* and others (see also below)
Indication: Thrombosis, embolism, atherosclerosis, homocysteinemia
TAT: approx. 2 days up to 1 week
Methods: Real-time-PCR (LightCycler technique), PCR, PCR-RFLP

Angiotensin converting enzyme (ACE)

OMIM: 106180

- Gene: *ACE*, locus 17q23
- Method: PCR, genotyping of the deletion/insertion polymorphism in intron 15 of the ACE-gene

ß-Fibrinogen-gene

OMIM: 134830

- Gene: *FGB*, Locus 4q28
- Method: PCR-RFLP, genotyping of the polymorphism c.-455G>A in the *FGB*-gene

Factor V

OMIM: 227400

- Gene: *F5*, locus 1q23
- Method: Real-time-PCR (LightCycler technique), genotyping of the polymorphism p.Arg506Gln in the *F5*-gene (Leiden mutation, APC resistance); and PCR-RFLP, genotyping of the polymorphism p.His1299Arg in the *F5*-gene

Factor XIII-gene

OMIM: 134570

- Gene: *F13A1*, locus 6p25-24
- Method: PCR-RFLP, genotyping of the polymorphism p.Val34Leu in the *F13A1*-gene

Glycoprotein Ia-gene, ITGA2

OMIM:192974

- Gene: GP Ia (*ITGA2*), locus 5q23-q31

- Method: Real-time-PCR (LightCycler technique), genotyping of the polymorphism c.759C>T (legacy c.807C>T) in the *ITGA2*-gene

Glycoprotein IIIa-gene, ITGB3

OMIM: 173470

- Gene: GP IIIa (*ITGB3*), locus 17q21.32
- Method: Real-time-PCR (LightCycler technique), genotyping of the polymorphism HPA-1a/1b c.176C>T; p.Leu59Pro (legacy c.1565C>T; p.Leu33Pro) in exon 2 of the *ITGB3*-gene

Methylenetetrahydrofolate reductase, MTHFR

OMIM: 236250

- Gene: *MTHFR*, locus 1p36.3
- Method: Real-time-PCR (LightCycler technique), genotyping of the mutations c.665C>T (legacy: c.677C>T) (p.Ala222Val) and c.1286A>C (legacy c.1298A>C) (p.Glu429Ala) in the *MTHFR*-gene

Plasminogen-Activator-Inhibitor type 1, PAI1

OMIM: 173360

- Gene: *PAI1* (*SERPINE1*), locus 7q21.3-22
- Method: Real-time-PCR (LightCycler technique), genotyping of the polymorphism 4G/5G (c.-675delG) in the *PAI1*-gene

Prothrombin / Factor II

OMIM: 176930

- Gene: *F2*, locus 11q11
- Method: Real-time-PCR (LightCycler technique) genotyping of the polymorphism g.20210G>A in the 3´UTR of the *F2*-gene

Short stature

Achondroplasia (Disproportionate short stature)

OMIM: 100800

- Gene: *FGFR3*, locus 4p16.3
- inheritance: autosomal dominant

- Indication: disproportionate short stature, short limbs, frontal bossing, mid face hypoplasia, lumbar lordosis, short fingers
- TAT: approx. 1-2 weeks
- Methods:
  1st tier: PCR and sequencing analysis of exon 9 of the *FGFR3* gene, detection of the mutations c.1138G>A and c.1138G>C
  2nd tier: PCR and sequencing analysis of exons 2-8 and 10-18 of the *FGFR3* gene

Hypochondroplasia (Disproportionate short stature)

OMIM: 146000
- Gene: *FGFR3*, locus 4p16.3
- inheritance: autosomal dominant
- Indication: disproportionate short stature, slight lumbar lordosis, reduced extensibility of the elbows, symptoms similar to achondroplasia but milder appearance.
- TAT: approx. 1-2 weeks
- Methods:
  1st tier: PCR and sequencing analysis of exon 12 of the *FGFR3* gene; detection of the mutations c.1620C>A, c.1620C>G, c.1619A>C and c.1619A>G
  2nd tier: PCR and sequencing analysis of exons 2-11 and 13-18 of the *FGFR3* gene

Thanatophoric dysplasia (Disproportionate short stature)

OMIM: 187600
- Gene: *FGFR3*, locus 4p16.3
- inheritance: autosomal dominant
- Indication: usual perinatal or neonatal lethal condition; short ribs and narrow thorax, macrocephaly, hypotonia, type I characteriued by micromelia and bent femurs, type II characterized by micromelia, straight femurs cloverleaf skull deformity
- TAT: approx. 1-2 weeks
- Method: PCR and sequencing analysis of *FGFR3*

SHOX-Related Growth Disorders

OMIM: 312865

- Gene: *SHOX/SHOXY*, locus Xpter-p22.32 / Ypter-p11.2
- Inheritance: pseudo-autosomal dominant
- Indication: idiopatic short stature, Leri-Weill syndrome, Langer mesomelic dysplasia
- TAT: approx. 2 weeks
- Methods: Detection of point mutations and large deletions/duplications
  1st tier. large deletion/duplication analysis (MLPA) of *SHOX* and PAR1
  2nd tier: PCR and sequencing analysis of *SHOX*

Uniparental disomies

Uniparental disomy 6, 7, 11, 14, 15

- UPD6: OMIM 601410
- UPD7: OMIM 180860
- UPD11: OMIM 130650
- UPD14: OMIM 608149
- UPD15: OMIM 105830, 176270
- Indication: Beckwith-Wiedemann syndrome; Silver-Russell syndrome; PWS/AS; neonatal diabetes mellitus
- TAT: approx. 2 weeks
- Method: microsatellite analysis, segregation analysis
- Parents' sample required

Paternity testing

- 16 polymorphic STRs in the human genome
- Indication: Paternity and/or maternity testing, twin testing for identical twins
- TAT: approx. 1-2 weeks
- Method: PCR, microsatellite analysis

Cytogenetics and molecular cytogenetics

Prenatal chromosome diagnostics

Chromosome analysis of amniotic fluid

- Indication: Advanced maternal age, conspicuous ultrasound and/or biochemical findings, fetal malformation, parental chromosomal structural changes, preceding abortion or stillbirth, birth of children with chromosomal changes, birth of children with congenital malformations, mutagen exposure before or during pregnancy, psychological distress, neural tube defects, viral infections of the embryo
- TAT: Approx. 1-2 weeks
- Material: Amniotic fluid
- Quantity: Approx. 10-15 ml, sealed original syringe, not centrifuged
- Methods: Cell culture of amniotic cells, preparation of chromosomes, G-banded chromosome analysis

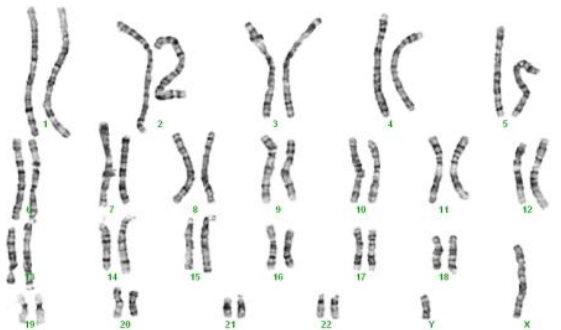


Figure: Inconspicuous male chromosomes (karyotype: 46,XY)

Chromosome analysis from chorionic villi sampling (CVS)

- Indication: Early prenatal diagnostics (from the 10th week of pregnancy), advanced maternal age, preceding abortion or stillbirth, parental chromosomal structural changes, conspicuous first-trimester-screening, conspicuous ultrasound findings, birth of children with congenital malformations, mutagen exposure before or during pregnancy, psychological distress, known familial gene mutations
- TAT: Rapid diagnosis after 6-24 hrs, final diagnosis 1-2 weeks
- Material: Chorionic villi biopsy
- Quantity: 10-20 mg, in transport medium or in sterile heparin-added physiological NaCl-solution
- Method: Direct preparation or preparation after 24 hrs-culture, long-term culture to rule out a placenta-fetus-mosaic und to assess the fine structure of chromosomes, preparation of chromosomes, G-banded chromosome analysis

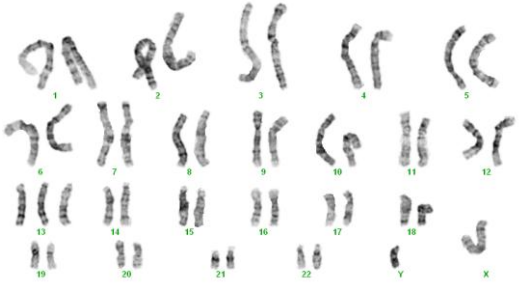


Figure: Male chromosomes with an additional chromosome 13 (trisomy 13)(karyotype: 47,XY,+13)

Postnatal chromosome diagnostics

Chromosome analysis of peripheral lymphocytes

- Indication: Unfulfilled desire to have children, sterility, suspicion of gonosomal chromosome changes, habitual miscarriages, birth of children with chromosome abnormalities, conspicuous prenatal karyotype of the unborn child, suspicion of a dysmorphic syndrome indicated by prenatal ultrasound findings, known familial chromosomal changes
- TAT: Approx. 1-2 weeks
- Material: 2-5 ml heparin-blood
- Method: Culture of peripheral T-lymphocytes (48 hrs, 72 hrs), G-banded chromosome analysis

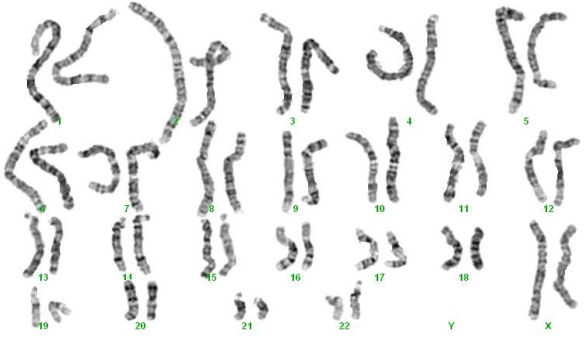
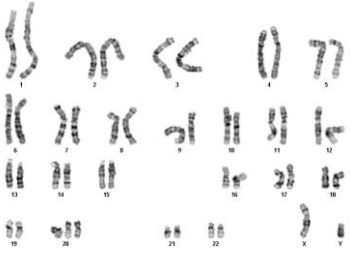


Figure: Inconspicuous female chromosomes (karyotype: 46,XX)

Chromosome analysis from products of conception

- Indication: Unfulfilled desire to have children, miscarriages after IVF/ICSI, preceding miscarriages, known parental chromosome changes, preceding births of children with chromosomal changes
- TAT: Approx. 1-3 weeks
- Material: Products of conception, 2-5 ml EDTA-blood from the mother
- Method: Cell culture, G-banded chromosome analysis. If the analysis reveals a normal female karyotype microsatellite analysis is performed to determine whether 46,XX results are truly representative of the fetal karyotype. If the cell cultures fail, we perform fluorescence in situ hybridization (FISH) with specific probes on native embryonic cells.



Left figure: Verification of a trisomy 22 after fluorescence in situ hybridization in native cells of chorionic villi preparations from products of conception (chromosome 22: gold, chromosome 13: red, chromosome 21: green, chromosome 16: aqua).
Right figure: Male chromosomes with a trisomy 20 (karyotype: 47,XY,+20)

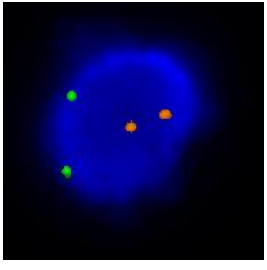
Molecular cytogenetics

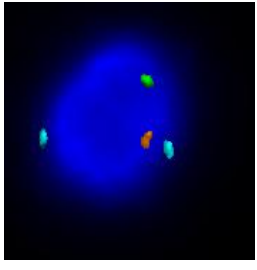
Fluorescence in situ hybridization (FISH)

Rapid prenatal diagnostics

- Chromosomal locations: 13q14 (RB1), 21q22 (DSCR), 18p11-q11 (D18Z1), Xp11-q11 (DXZ1), Yp11-q11 (DYZ3)
- Indication: Advanced maternal age, conspicuous ultrasound and/or biochemical findings , psychological distress (IGEL-services)
- TAT: Approx. 4-24 hrs
- Material: Uncultured amniotic cells
- Method: Preparation of native amniotic cells, prescreening for the most frequent aneuploidies with fluorescence in situ hybridization using specific probes for chromosomes 13, 18, 21, X, and Y

The prenatal FISH test is always performed in combination with conventional chromosome analysis.

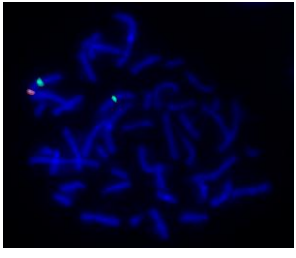


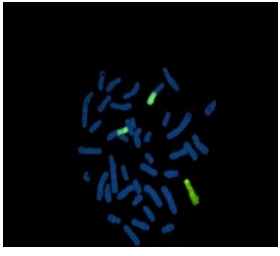


Left figure: Inconspicuous signal pattern in a native amniotic cell after a fluorescence in situ hybridization with specific probes for chromosomes 21 (red) and 13 (green)
Right figure: Inconspicuous male signal pattern after hybridization with specific probes for chromosomes 18 (aqua), Y (red), and X (green)

Mikrodeletion-diagnostics, Screening for mosaics, „chromosome painting"

- Chromosomal locations: Depend on the indication and preliminary findings, e.g., Wolf-Hirschhorn-syndrome (4p16.3), Cri-du-Chat (5p15.2), Williams-Beuren syndrome (7q11), Prader-Willi / Angelman syndrome (15q11-q13), Lissencephaly / Miller-Dieker syndrome (17p13.3), Smith-Magenis syndrome (17p11.2), DiGeorge / Catch22 syndrome (22q11.2), Kallmann syndrome (Xp22.3), sex reversal (Yp11.23), X-linked Ichthyosis, and others on request
- Indication: Suspected microdeletion syndrome, chromosomal translocation, exclusion of mosaics, complex chromosomal rearrangements, detection of a familial microdeletion (e.g. chromosomal rearrangement under participation of the chromosome region critical for Down syndrome)
- TAT: Approx. 1-5 days
- Material: Heparin blood, amniotic fluid, chorionic villi, products of conception, buccal swabs, skin biopsy
- Method: Cell culture, preparation of chromosomes, hybridization with appropriate fluorescence-marked DNA-probes, analysis under the fluorescence microscope





Left figure: Confirmation of a deletion of the SHOX-region (red signal) in the short arm of one of the two X chromosomes using FISH
Right figure: Presentation of a balanced reciprocal translocation between chromosomes 4 and 6 after FISH with a „painting" probe specific for chromosome 4 (green signal)

Subtelomere analysis

- Location of FISH probes: Subtelomere-regions of all chromosomes
- Indication: Suspicion of chromosomal dysmorphic syndrome of unclear origin, developmental retardation, mental retardation, phenotypic features, habitual miscarriages
- TAT: Approx. 1-2 weeks
- Material: 2-5 ml heparin blood
- Method: Fluorescence in situ hybridization with subtelomere-specific probes (whole panel) always in context with a conventional chromosome analysis, single probe diagnostic on request

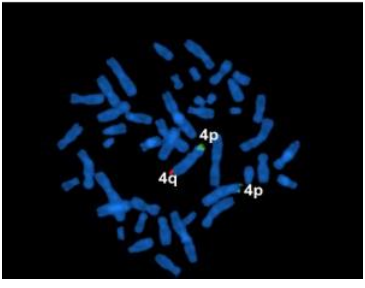
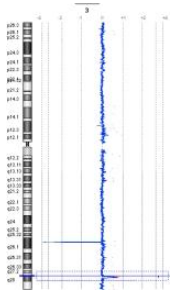
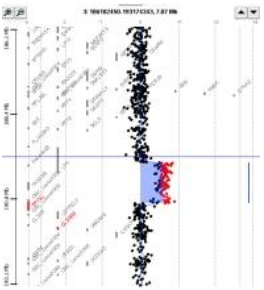


Figure: Confirmation of a deletion in the subtelomeric region of the long arm of one chromosome 4 (red signal in 4q)

Array CGH diagnostics

- Indication: Mental retardation, pre- and postnatal growth retardation, specific growth anomalies (e.g. microcephaly, microsomia or macrocephaly, macrosomia),two or more facial dysmorphies (e.g., hypertelorism, nose- and ear anomalies), congenital anomalies (e.g. heart defect, hand defects, hypospadias), cerebral seizures, behavioral abnormalities
- TAT: Approx. 2-6 weeks
- Material: 3-5 ml fresh EDTA blood; To validate detected imbalances an additional heparin blood sample (3-5 ml) might be needed; To clarify the origin of a detected imbalance, parental blood samples (3-5 ml heparin or EDTA blood) might be necessary.
- Method: Comparative genomic hybridization on the array, detection of genomic imbalances in the whole genome





Left figure: Scatter plot view of an interstitial duplication in the long arm of chromosome 3 (3q28)
Right figure: Zoomed gene view, focused on a 7 Mb window, which contains the duplication (region marked in blue)

Quality assurance

Our Quality Management System is based on regular internal and external Quality Assessment Schemes. As a consequence, we have established quality control procedures which not only comply with the highest quality standards but which also guarantee a continuous improvement of our quality procedures. Since the establishment of our laboratory in the year 2000 one of our most important quality control procedures is the regular participation in the ring trials of the Association of German Human Genetics Laboratories e.V. (BVDH e.V.).
In this way, quality, safety and reliability of our services are assured to be on the highest level for the benefit of the patients.

Department of Molecular Genetics
The Department of Molecular Genetics successfully participates on regular basis in inter-laboratory tests of the European Network of Cystic Fibrosis, the German Society of Clinical Chemistry and Laboratory Medicine (DGKL), inter-laboratory tests of the European Molecular Genetics Quality Network (EMQN), inter-laboratory tests of the Society for Promotion of the Quality Assurance of Medical Laboratories (INSTAND e.V.) as well as in exchange of test samples with cooperating laboratories:
Angelman / Prader Willi syndrome
AZF
Breast-ovarian cancer, familial (BRCA1, BRCA2)
Congenital adrenal hyperplasia (CAH)
CMT
Cystic fibrosis
DNA-sequencing
DMD/BMD
FAP
Factors associated with thrombosis (factor II, V, MTHFR, and others)
Fragile X- syndrome
Gilbert syndrome
Hemochromatosis
HLAB27
HNPCC
Huntington disease
Hypercholesterinemia (LDLR, APOB, APOE)
LHON
Optic atrophy

MEN2
Microdeletions Y-Chr. (AZF)
MODY
Myotonic dystrophy type I
NAT2
Osteogenesis Imperfecta
Periodic fevers
Pharmacogenetics (TPMT, DPD and others)
Paternity testing
PKU
SMA
Thalassemia, α- and ß-
Von-Hippel-Lindau syndrome
Wilson disease

Department of Cytogenetics
Our internal Cytogenetics standards in the pre- and postnatal specialities are assessed on a regular basis with the participation in inter-laboratory tests of the EQA (European Quality Assessment) and the BVDH e.V. (Association of German Human Genetics Laboratories e.V.). The assessment schemes evaluate the speed of the examination as well as the resolution of the chromosomal preparations. In the years 2005 to 2009 our laboratory was rated among the 10 best laboratories in Germany with regards to speed of examination and quality of chromosomal analysis. In 2006 our laboratory was invited by the BVDH e.V. to participate at the European Pilot Study of Cytogenetics Quality Assurance.

DAkkS – Accreditation

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Our Laboratory is accredited by the "DAkkS" (Deutsche Akkreditierungsstelle GmbH). All Molecular Genetic and Cytogenetic examinations are accredited according to DIN EN ISO 15189:2007. All examinations for Paternity Testing are accredited according to DIN EN ISO/IEC 17025:2005.