Clinical and genetic tests and focus

Clinical and genetic test	A Test in Focus	Response timelines
Clinical exome (WES) for all genetic conditions with clinical interpretation	Genando S.r.l. currently offers WES clinical interpretation mostly for TRIOS. With current technology, we can analyze approximately 96% of the exome, which includes approximately 99% coverage for over 4,500 genes previously associated with the disease. The broad interpretation of the clinical data provided with our comprehensive medical reports includes differential diagnostic approaches and a detailed interpretation of key findings. Our clinical reporting involves: • Evaluation of clinical information • Detailed description of the method • Clear results of identified variants according to the international best-practice guidelines (Clinical Laboratory Improvement Amendments of 1988 – CLIA, College of American Pathologists -CAP- and American College of Medical Genetics and Genomics- ACMG, European Society of Human Genetics- ESHG, and Società Italiana di Genetica Umana- SIGU. • Comprehensive medical interpretation with differential diagnostic approaches, if applicable • References to publications supporting the medical and scientific results • Recommendations for follow-up analyses for specific diseases • Coverage reports of genes	4 weeks (it may take longer in complex cases where a full clinical interpretation is required)

	The report will contain results that could explain the cause of current medical problems that lead the physician to suggest this test. The test may also contain information on genes and diseases that have clear and immediate medical significance for the health of the proband and health of family members, regardless of whether they refer to current symptoms.. As part of the TRIO WES analysis, we will report the findings in genes that have occurred in the individual concerned, but not in the asymptomatic parents. This category of results caused by *de novo* findings, can be significant in determining the cause of the medical condition. Therefore, this category of variants will be reported for genes with or without a known current association with the disease. We will also report variants heterozygous or homozygous compounds in genes where each parent has a variant and the affected individual has inherited both, for genes with a known association with the disease. It is important to note that the clinical report of WES may contain information on diseases and genes that do not refer to the proband (parents) current condition, but are considered "secondary finding" from a medical point of view, according to current knowledge and based on the ACMG and ESHG recommendations. The test requires 5-10 cc of whole blood (*EDTA* tubes).	
Exome clinical interpretation	Genando S.r.l. currently it can also offer WES clinical interpretation. Customers **must** provide three WES report (proband, biological mother, and biological father) to complete this order. Without providing the TRIO sequencing report, in most cases it is very difficult to obtain a precise clinical interpretation. In case of sequencing of the "single index case", **complete clinical information** (clinical record and complete phenotypic description) is required. Patients who consent to receive medically actionable secondary findings are evaluated for pathogenic and probably pathogenic variants recommended by ACMG. Variants of uncertain significance (VUS) in these genes are not reported. Parental origin of reportable variants is declared. Variants present in a parent but absent from the proband are not evaluated.	2 weeks

Exome sequencing (WES) report (vcf file or genetic variants prioritization file)	An interpretive report will be provided including rare probably causative variants (MAF <1%) of proband. This report will send in these cases: - No clinical features reported by the patient - Non-availability of the trio - Direct customer request It is possible to include medically actionable secondary findings (unless the patient opts out) according to the ACMG indications. The test requires 5-10 cc of whole blood (*EDTA* tubes)	4 weeks
Prenatal WES and clinical interpretation Fetus and parents (Prenatal Trio WES)	Genando S.r.l. performs prenatal WES on placental DNA after CVS or fetal DNA after amniocentesis. Furthermore, it can also be performed on the cell-free fetal DNA (cff-DNA) in the maternal circulation. Genando S.r.l. can specify the amount of material needed. **The DNA from the placenta/fetus is analyzed together with DNA from both parents** ("WES TRIO-analysis"). Parental samples are used in filtering fetal data based on expected inheritance. Parental samples are not analyzed individually for genetic disease and the result/report on parents is provided in the same document. The description of the fetal phenotype is essential for the achievement of a possible diagnosis; without the precise description of the ultrasound, important variants for diagnosis could be lost or some SNVs could be misinterpreted. WES may detect single nucleotide variants (SNV) but not deletions and duplications. **Therefore, SNP/CGH array must always be performed before WES**. The SNP/CGH array together with WES can therefore provide a diagnosis in around 50% of cases. Furthermore, technical limitations imply that repeated expansions, 1-2 deletions of exons within genes and SNVs in poorly covered regions are not detected. This implies that a normal result after prenatal WES reduces, but does not eliminate the risk of a genetic disease in a fetus with precise malformations/indications. The probability of finding a significant genetic variant depended on the number of malformations (single, 22.3 % versus multiple, 30.8 %) and the organ system involved [skeletal (30 %), urogenital (23.1%), dysmorphic (23.5 %), CNS (23.1 %), cardiovascular (20.6 %) and gastrointestinal (none)]. **Fetuses with sonographic soft markers have no indications for the WES analysis**.	4 weeks

	Important: If the patient requires prenatal WES without any specific clinical indications or a positive family history for specific diseases, **only SNV will be reported that are known in the literature as being associated with disease in large well-characterized patients 'cohorts**. **Important: in order to carry out WES on cf-DNA, about 15 cc (2 tubes) of whole maternal blood are required, collected in specific "Cell-Free DNA Collection Tubes".**	
Prenatal exome sequencing report (vcf file or genetic variants prioritization file)	A report will be provided that includes rare variants with MAF <1%, without clinical interpretation. Sample of parents is always requested. The test requires 5-10 cc of whole blood (*EDTA* tubes)	4 weeks
Trio WES prenatal and post-natal with interpretation and clinical report	Genando S.r.l. currently offers a clinical interpretation WES mainly for TRIOS. Patient physicians **must** provide three samples (proband, biological mother and biological father) to complete this order. WES is more suitable for people with: - Complex phenotypes with multiple differential diagnoses - Genetically heterogeneous disorders - Suspicious genetic disorders in which a specific genetic test is not available - Previous inconclusive genetic testing - Fetal malformation This test differs from other genetic tests because the proband (or affected individual) is tested together with his parents and the results interpreted as a family. **This test approach can be helpful for identifying the genetic causes of a medical condition**. Analysis of data for changes occurring in the proband, but not in the parents, can help to identify new mutations in the genes that can be causal (*de novo* variant). In other cases, the inheritance of changes from parent (s) to proband can also help in the identification of potentially causative disease genes. The decision to undergo the TRIO WES test is taken by patients and their physicians. In general, the test is used when medical history and physical examination strongly suggest that there is a genetic cause for your medical problems.	4 weeks

	The clinical history and the precise phenotype are required and essential for correct clinical interpretation. The report will contain results that could explain the cause of current medical problems that lead the physician to suggest this test. The test may also contain information on genes and diseases that have clear and immediate medical significance for the health of proband and health of family members, regardless or whether they refer to current symptoms. As part of the TRIO WES analysis, we will report the findings in genes that have occurred in the affected individual, but not in the asymptomatic parents. This category of results caused by *de novo* findings, can be significant in determining the cause of the medical condition. Therefore, this category of variants will be reported for genes with or without a known current association with the disease. We will also report compound heterozygous or homozygous variants in genes in which each parent has a variant and the affected individual has inherited both, for genes with a known association with disease. It is important to note that the clinical report of WES may contain information on diseases and genes that do not relate to current proband (parents) condition, but are considered **"secondary finding" medically actionable**, according to current knowledges and based on the ACMG and ESHG recommendations. The test requires 5-10 cc of whole blood for each sample (proband and parents) on *EDTA* tubes.	
SNP/CGH array on amniotic liquid and CVS	Genando S.r.l. suggests that resolution of SNP array analysis in Prenatal Diagnosis **does not exceed 180k**, in line with the Joint Position Statement from the International Society of Prenatal Diagnosis (ISPD), the Society of Maternal Fetal Medicine (SMFM) and the Perinatal Quality Foundation (PQF) and with the indications SIGU/SIEOG (Italian Society of Obstetric and Gynecological Ultrasound). In this way we avoid having results that are not immediately interpretable, which increase with increasing diagnostic sensitivity on our genome. The 180k resolution allows to explore in high resolution about 500 genomic regions, of which about 390 are associated with congenital malformations and intellectual disability syndromes. The rest of the genome is analyzed with a real average resolution of about 80 Kb. With this resolution, it is also possible to identify of up to 10% of chromosome mosaicisms.	8 working days

	Since the identified variants can be *de novo* or inherited, for a more correct interpretation of the CGH/SNP-array data it is sometimes necessary to carry out the examination also on the parents (for this reason a peripheral blood sample will be required for both parents at the time of invasive procedure amnio/villocentesis). The test requires 5-10 cc of whole blood (*EDTA* tubes) for the parents	
SNP/CGH array on peripheric blood and abortive tissue	Several studies have shown that, compared to the karyotype, the array technology increases the diagnostic yield in cases of intrauterine fetal death (IUFD) or fetal mortality or abortions. These studies demonstrated the additional value of the array test compared to the karyotype: this test provides a relative increase in the diagnosis of genetic abnormalities of 41.9% in all stillbirths, 34.5% in fetal deaths and 53.8% in stillbirths with anomalies. Because culture failures due to lack of cell growth or maternal cell contamination are well-known problems in fetal mortality, **the Genando laboratory also obtained more effective diagnoses using SNP array on DNA extracted directly from non-cultured fetal material**, rather than the karyotype after culture. For this type of test, we could also use SNP arrays with higher resolution, which we will evaluate on the clinical history of each case. Since the identified variants can be *de novo* or inherited, for a more correct interpretation of the CGH/SNP-array data it is sometimes necessary to carry out the exam also on the parents (for this reason a peripheral blood sample will be required for both parents). The test requires 5-10 cc of whole blood (*EDTA* tubes) with the abortive tissue sample	20 working days
NIPT	The Non-Invasive Prenatal Test (NIPT) that Genando S.r.l. proposes, in addition to the classical aneuploidies of chromosomes 21, 18, 13, X and Y, **it can also detect unbalanced anomalies in the structure of all chromosomes**, such as duplications or deletions of some DNA regions, up to about 3 Mb (megabases). In this way we can guarantee the screening of all the most frequent microdelection/ microduplication syndromes. This test is performed on a single maternal blood sample and combines the latest next generation sequencing technology with the highest quality medical reporting	5-7 working days

Karyotype on lymphocyte	The blood cell karyotype method has been developed to provide information on chromosomal abnormalities. The standard karyotype is performed with a 450-550 band level. The test requires 3-5 cc of whole blood (*Lithium Heparin Tubes* tubes).	30 working days
Gene panels (NGS) (e.g. solid tumor and hematopoietic tumor, cardiomyopathy, deafness, eyes-diseases, diabetes, etc)	Our panels include over 2600 genes selected based on edited gene reviews, variant databases (such as HGMD, ClinVar, etc), most recent literature, and customer inquiries. Genando S.r.l. it offers optimized diagnostic yields, enhanced differential diagnosis, up to date scientifically validated genes across all our panels and enhanced clinical utility. The genes are covered with high quality, allowing a true diagnostic impact in cases of difficult patients. Our panels cover all medical specialties. We offer Sequence Analysis and Targeted Del/Dup (CNV) analysis for about all panels. Panels can be customized by adding genes from our single gene list or by removing genes from the selected panel. Our panels contain covered genes ≥20x. The test requires 5-10 cc of whole blood (*EDTA* tubes).	15 working days

Genando S.r.l. uses for laboratory analysis a wide range of methods, all with high technological content.

Test ID: WES

One consequence of WES analysis is the greater amount, complexity, and variety of results that need to be interpreted. It is therefore of utmost importance to obtain detailed clinical information from the index patient and the parents (TRIO) before the execution of the exome sequencing.

Not providing any clinical or medical information – including your patient's family history – can affect test results and their interpretation. **Missing clinical information could lead to the exclusion of genetic variants that could be relevant to the patient.**

Requirement for Parental Samples.
As part of the Trio WES test, blood samples from the proband's biological parents are required. Trio Whole exome sequencing (Trio WES) will be performed simultaneously on the proband and parental samples and the sequence data will be analyzed in the context of family relationships. Parental data will be used to help interpret proband data. A separate parental report will be issued as regards the categories of incidental findings.

We provide patients with the most informed clinical report on the market. Clinical interpretation requires a fundamental clinical and genetic understanding. At Genando S.r.l. our geneticists and clinicians, who together evaluate the results of the sequence analysis pipeline in the context of the information on the phenotype provided in the request, prepare the clinical interpretation. Our goal is to provide clinically meaningful statements that are comprehensible to all medical professionals, even without genetic training.
In our clinical report, we provide a comprehensive description of our rationale for classifying the variant. The variants listed are always classified using the "Genando Variant Classification Scheme" which was developed by evaluating existing literature, databases and with thousands of clinical cases analyzed in our experience.
We constantly follow the genetic literature by adapting new relevant information and results to our diagnostics. These processes ensure that our analysis and clinical interpretations remain the most up-to-date on the market.

Because WES covers all protein-coding genes of the genome, it allows the detection of variants that are not associated with the indication for sequencing ordering but that are of medical value for patient care. These type of results are called “secondary or incidental findings”. We follow the ACMG Recommendations for the Reporting Incidental Findings in Clinical Exome Sequencing to seek and report clinically actionable mutations of specified types in genes (approximately 56 currently) determined by the ACMG, if the patient opted for analysis and these are "actionable findings". If parents or other family members are also subjected to WES, they also have the option to opt-in for reporting secondary findings. The secondary findings are showed in a separate section of the document and variants shown are confirmed using Sanger sequencing, based on the indication of guidelines
The WES examination must be requested by a physician and must be accompanied by an informed consent form and detailed clinical information.
In this regard and to facilitate the collection of clinical data, a diagram for the compilation of the "clinical path" in this specific site (https://www.genando.com/eforms/test-genando-grecia/70/) is available.

As medical information continues to advance, it is important to know that the interpretation of the variants is based on the information available at the time of testing and may change in the future.
The patient's sample will have certain findings confirmed by a second methodology (Sanger sequencing) as the recommendations ACMG, ESHG and SIGU.
This test does not detect mitochondrial DNA variants.

Report Exclusions: The report will not include findings of genes that cause adult onset dementia syndromes or neurodegenerative disorders for which there is currently no prevention or cure. However, if patients had a clinical presentation that could indicate such a disorder or a mixed neurological phenotype, the results may be returned for genes that have an allelic association with dementia, or dementia is a component of the phenotype will then be reported in the proband and the parents.

We expect to find hundreds of variations comparing the DNA to the reference sequence, most of these do not relate to the disease and therefore will not be reported.
The raw sequence data generated by the TRIO WES is available for request after a WES report is issued.

Potential Risks

- It is possible that the proband (or parents) may have a variant in a gene included in the WES test, but the WES test was not able to detect the variant. Therefore, it is possible that the patient may be affected by one of the conditions tested by WES, but that the test did not detect the condition.
- The results may not be clear or indicate the need for further tests on other family members.
- The WES test does not analyze 100% of the genes in the human genome. There are some genes that cannot be included in the test due to technical reasons.
- It is possible that additional information may come to light during these studies concerning family relationships. For example, data may suggest that family relationships are not as reported, such as non-paternity (the father of the individual is not the biological father) or consanguinity (marriage or reproductive partners are more or less close relatives). If a discrepancy is identified, we will notify through the physician.
- If the patient signs the consent form, but no longer wishes to have the sample tested, the physician must inform Genando, to cancel the test. If the test is complete because two weeks have elapsed since the sample was sent, the full cost of the will be charged.
- The cumulative results of the WES tests on many samples can be published in the medical literature. These publications will not include any information that will personally identify each subject analyzed.
- Due to the fact that many different genes and conditions are analyzed, there is a risk that genetic information may be learned that is not directly related to the reason for ordering the WES. This information could concern diseases with symptoms that may develop in the future or in other family members, as well as conditions that have no treatment. <u>The results will not include this information</u>.

Due to the complex nature of the WES and TRIO WES tests, families are recommended to. implement genetic counseling together with tests.

Test ID: SNP/CGH array

In clinical diagnostics, both array comparative genomic hybridization (array CGH) and single nucleotide polymorphism (SNP) genotyping have proven to be powerful genomic technologies used for the evaluation of developmental delay, multiple congenital anomalies, and neuropsychiatric disorders. Although the resolution of a single exon across the genome is not feasible for SNP arrays, SNP arrays show greater sensitivity for the detection of low-level mosaic aneuploidies and chimerism and offer the ability to detect copy number neutral regions of absence of heterozygosity (AOH). Consanguinity can be detected by AOH, since it is expected that more regions of AOH are present in individuals from inbred populations, which represent identical chromosomal segments by lineages after transmission through parental lineages. The size and number of AOH blocks are related to the degree of kinship of the parents. Researchers and clinicians are also using the location of homozygous regions to map information into consanguineous families to identify genes that causes autosomal recessive disease.

When confined to a single chromosome, AOH regions may indicate uniparental disomy (UPD). Although the true prevalence of UPD is not known, there is expected to be at least ~1 out of 3500 live births based on the information available in the 'pre-genome analyses era'. UPD is a well-known mechanism that leads to human disease if a chromosome containing imprinted genes is involved or if there is a recessive mutation that causes the disease. Moreover, it is also possible to detect CNV, as in "classical CGH-array".

Literature data show that the array techniques applied to Prenatal Diagnosis are able to identify unbalanced rearrangements with a frequency greater than 6-7% compared to the conventional karyotype, if there are ultrasound abnormalities, and with a frequency greater than 1-1.7 %, in the absence of ultrasound abnormalities.
Since the application of these technologies makes it possible to identify a greater number of pathologies deriving from chromosomal rearrangements, **their use is strongly recommended also in Prenatal Diagnosis**, especially in cases of increased nuchal translucency and in cases of malformations detected by ultrasound.

Test ID: NIPT
Non-invasive prenatal testing (NIPT) is a genetic test that using cell-free circulating fetal DNA in the maternal serum to currently screen for the most common fetal aneuploidies: trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome), trisomy 13 (Patau syndrome) and monosomy X (Turner syndrome). The DNA of the fetus is found circulating in the maternal blood. This DNA can be from two sources: intact fetal cells or from circulating cell-free fetal DNA (cff-DNA) from the breakdown of fetal cells that are mostly placental. Cff-DNA clears very quickly from the maternal system and is not detectable in maternal serum within a few hours of delivery. Therefore, cff-DNA detected during pregnancy is considered representative DNA of the current fetus.
NIPT shares features of both screening and diagnostic tests, although **it is currently more appropriately considered as a screening test**. The sensitivity and specificity for NIPT were assessed in more detail to detect trisomy 21 in high-risk women; in this clinical setting, the sensitivity of NIPT is 99.5% and the specificity is 99.9%. The sensitivity detected for trisomy 13 and 18 were more variable, with sensitivity up to 100% and specificity of 99.9%.
The incorporation of the NIPT into the current model for aneuploidy screening offers some additional benefits,, as well as additional choices, for women during the prenatal period. It has excellent performance characteristics for detection of Down syndrome, although it is currently not recommended as an autonomous diagnostic test. But is a diagnostic test for some different Mendelian diseases, and **Genando laboratory can offer this test as a diagnostic for some different monogenic conditions as well as for the screening of classic chromosomal aneuploidies**.
It is recommended that tests be performed in collaboration with obstetric specialists and, if necessary, clinical genetics services can adequately address additional reflections and tests and are skilled in providing counselling.

The chromosomal aneuploidies of a twin gestation can generally be detected by this test. However, the test cannot be attributed to individual twin fetuses because the sensitivity and specificity of twin gestations for the detection of aneuploidies are limited. In case of twin pregnancy and detection of only one Y chromosome by the test, the fetal gender of each individual twin cannot be determined by the test.

In the unlikely case of inconclusive results of NIPT due to system limitation, we recommend further follow-up of the fetal growth using ultrasound as well as 2nd trimester ultrasound screens. In case of abnormalities observed on the ultrasound examination or if there is a positive family history of fetal abnormalities or other genetic disorders, we strongly suggest invasive tests and subsequent analysis of CGH/SNP analysis or additional genetic tests.

Test ID: Gene Panels

The targeting of specific regions in the genome is necessary when looking for variants or trying to identify rearrangements in diseased tissues compared to normal tissues.

Genando S.r.l. use a hybrid-capture based method to enrich target genes. Various fixed and customized panels are available.

If the patient needs to investigate certain specific cardiac conditions, **Genando is able to offer targeted tests**: for example for aortic diseases such as aortic dissection (thoracic aorta), aortic aneurysm (ruptured, thoracic aorta), etc, analyzing a panel of 41 genes associated with this specific condition.

Genes with partial, or whole gene, segmental duplications in the human genome are expressly indicated, if they overlap with the UCSC pseudogene regions. The technology may have limited sensitivity to detect variants in genes with these characteristics.

This test does not detect the following:

- Complex inversions
- Gene conversions
- Balanced translocations
- Mitochondrial DNA variants
- Repeat expansion disorders
- Non-coding variants deeper than ±20 base pairs from exon-intron boundary

This test may not reliably detect the following:

- Low level mosaicism
- Stretches of mononucleotide repeats
- Indels larger than 50bp
- Single exon deletions or duplications
- Variants within pseudogene regions/duplicated segments

We provide patients (and physicians) with the most comprehensive clinical report available on the market. Clinical interpretation requires a fundamental understanding of clinical genetics and genetic principles. At Genando S.r.l, our PhD molecular geneticists and medical geneticists together prepare the clinical statement by evaluating the variants identified in the context of the phenotypic information provided in the application form and after completing the "clinical path" in this specific site (https://www.genando.com/eforms/test-genando-grecia/70/). Our goal is to provide clinically meaningful statements that are understandable for all medical professionals.

The final step in the analysis of sequence variants is the confirmation of **variants classified as pathogenic or probably pathogenic**.
The variants that meet all the following criteria are not confirmed by Sanger:

- the quality score of the variant is higher than the internal threshold for a true positive call
- an unambiguous IGV in-line with the variant call
- previous Sanger confirmation of the same variant at least three times at Genando.

The reported variants of uncertain significance are confirmed with Sanger sequencing only if the quality score is lower than our internally defined quality score for true positive call. The copy number variations reported with a size <10 exons are confirmed by orthogonal methods such as qPCR or high resolution SNP array if the specific CNV was seen less than three times at Genando.
The identification of pathogenic or probably pathogenic variants in dominant disorders or their combinations in different alleles in recessive disorders are considered molecular confirmation of the clinical diagnosis. In these cases, family member tests can be used to stratify the risk within the family. In the case of variants of uncertain significance (VUS), we do not recommend the stratification of the risk of the family members based on the VUS result. Furthermore, in the case of VUS, we do not recommend the use of genetic information in patient management or genetic counseling.
Our interpretation team has expertise in analyzing variants from thousands of individuals with rare diseases. Our laboratory is therefore in a good position to reclassify previously reported variants as soon as new information becomes available.

List of diagnostic services

Whole exome sequencing (WES) for:

• bone dysplasias and collagenopathies
• intellectual disability
• cardiomyopathies and cardio-vascular malformations
• cerebral malformations
• epilepsy

- solid tumors
- leukemic/myelodysplastic syndromes
- diseases of the red blood cell
- ectodermal dysplasias
- hypovision/blindness/retinal degeneration
- hearing loss/deafness
- urogenital malformations/Congenital Abnormalities of the Kidneys and of the Urinary Tract
- hepatic/respiratory/pancreatic insufficiency
- kidney failure/kidney diseases
- plurimalformative syndromes
- muscular degeneration disorders

NGS Panel Genomic (**Gene Panels)** for:

Cardiology
Long QT Syndrome (LQTS), Short QT Syndrome (SQTS), Brugada Syndrome, Arrhythmia, Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), Polymorphic Ventricular Tachycardia (CPVT), Atrial Fibrillation, Marfan Syndrome, Cardiomyopathy, Aorta Panel, Structural Heart Disease, Right Ventricular Cardiomyopathy (ARVC), Hypertrophic Cardiomyopathy (HCM), Dilated Cardiomyopathy (DCM), Ehlers-Danlos Syndrome, Hereditary Hemorrhagic Telangiectasia (HHT), Hyperlipidemia Core, Left Ventricular Non-Compaction Cardiomyopathy (LVNC), Heterotaxy and Situs Inversus, Liddle Syndrome, Noonan Syndrome, Pulmonary Artery Hypertension (PAH)

Dermatology
Albinism, Ectodermal Dysplasia, Cutis Laxa, Hereditary Acrodermatitis Enteropathica, Neurofibromatosis, Adams-Oliver Syndrome, Hermansky-Pudlak Syndrome, Dyskeratosis Congenita, Ehlers-Danlos Syndrome, Palmoplantar Keratoderma, Epidermolysis Bullosa, Progeria and Progeroid Syndromes, Pachyonychia Congenita, Waardenburg Syndrome

Ear, Nose & Throat
Branchio-Oto-Renal (BOR) Syndrome, Comprehensive Hearing Loss and Deafness, Non-Syndromic Hearing Loss, Syndromic Hearing Loss, Usher Syndrome, Alport Syndrome, Pendred Syndrome, Stickler Syndrome, Hereditary Hemorrhagic Telangiectasia (HHT), Waardenburg Syndrome

Endocrinology
Comprehensive Monogenic Diabetes, MODY, Monogenic Obesity, Hypoglycemia, Hyperinsulinism and Ketone Metabolism, Glucocorticoid Deficiency, Congenital Adrenal Hyperplasia, Hyperparathyroidism, Hypomagnesemia, Hypothyroidism and Resistance to Thyroid Hormone, Kallmann Syndrome, Premature Ovarian Failure, Abnormal Genitalia/ Disorders of Sex Development

Gastroenterology
Congenital Hepatic Fibrosis, Polycystic Liver Disease, Cholestasis Panel, Gastrointestinal Atresia, Congenital Diarrhea, Hirschsprung Disease, Pancreatitis

Hematology
Anemia, Diamond-Blackfan Anemia, Fanconi Anemia, Bloom Syndrome, Bone Marrow Failure Syndrome, Red Blood Cell Membrane Disorder, Hermansky-Pudlak Syndrome, Comprehensive Hematology Panel, Platelet Function Disorder, Thrombocytopenia, Congenital Neutropenia, Coagulation Factor Deficiency, Bleeding Disorder/Coagulopathy, Hemophagocytic Lymphohistiocytosis, Hereditary Leukemia, Dyskeratosis Congenita

Cancer
Comprehensive Hereditary Cancer Panel, Breast and Gynecological Cancer, Colorectal Cancer, Lung Cancer, Melanoma and Skin Cancer, Gastrointestinal Cancer, Leukemia, Endocrine Cancer, Pancreatic Cancer, Paraganglioma-Pheochromocytoma, Renal Cancer, Hereditary Pediatric Cancer, Tuberous Sclerosis, Cerebral Cancer, Xeroderma Pigmentosum, Neurofibromatosis

Immunology
Chronic Granulomatous Disease, Congenital Neutropenia, Primary Immunodeficiency (PID), Severe Combined Immunodeficiency, Primary Ciliary Dyskinesia (PCD), Autoinflammatory Syndrome, Bone Marrow Failure Syndrome, Complement System Disorder, Dyskeratosis Congenita, Hemophagocytic Lymphohistiocytosis

Malformations
Panel Chondrodysplasia Punctata Panel Cleft Lip/Palate and Associated Syndromes, Comprehensive Growth Disorders / Skeletal Dysplasias and Disorders, Comprehensive Short Stature Syndrome, 3-M Syndrome/Primordial Dwarfism, Seckel Syndrome, Cornelia de Lange Syndrome, Adams-Oliver Syndrome, Macrocephaly/Overgrowth Syndrome, Microcephaly and Pontocerebellar Hypoplasia, Brachydactyly/Syndactyly, Meier-Gorlin Syndrome, Comprehensive Skeletal Dysplasias and Disorders, Exostosis and Related Disorders, Amelogenesis Imperfecta and Dentinogenesis Imperfecta, Arthrogryposes, Craniosynostosis, Facial Dysostosis and Related Disorders, Septo-Optic Dysplasia, Osteogenesis Imperfecta, Osteopetrosis and Dense Bone Dysplasia, Cerebral Cavernous Malformation, Gastrointestinal Atresia, Heterotaxy and Situs Inversus, Hirschsprung

Disease, Kabuki Syndrome, Holoprosencephaly, Neuronal Migration Disorder, Lissencephaly, Polymicrogyria, Limb Malformations, Neurofibromatosis, Spondylometaphyseal/Spondyloepi-(meta)-physeal Dysplasia, Skeletal Dysplasia with Abnormal Mineralization, Skeletal Dysplasias Core, Short Rib Dysplasia/Asphyxiating Thoracic Dysplasia, Metaphyseal Dysplasia Micromelic Dysplasia, Vascular Malformations, Lymphatic Malformations and Related Disorders

Metabolic Disorders

Congenital Disorders of Glycosylation, Glycogen Storage Disorder, Peroxisomal Disorders, Coenzyme q10 Deficiency, Cystinuria, Hyperphenylalaninemia, Hyperinsulinism and Ketone Metabolism, Hypoglycemia, Panel Mitochondrial DNA Depletion Syndrome, Congenital Mono- and Disaccharide Disorders, Monogenic Obesity, Nonketotic Hyperglycinemia/Glycine Encephalopathy, Aicardi-Goutières Syndrome, Congenital and Familial Lipodystrophy, Hypomagnesemia, Organic Acidemia/Aciduria & Cobalamin Deficiency, Purine and Pyrimidine Metabolism Disorders, Creatine Metabolism Deficiency, Lysosomal Disorders and Mucopolysaccharidosis Panel Metabolic Liver Failure, Fatty Acid Oxidation Syndrome, Hereditary, Hemochromatosis Homocystinuria, Porphyria, Hyperammonemia and Urea Cycle Disorder, Metabolic Myopathy and Rhabdomyolysis, Periodic Paralysis, Nephrolithiasis, Tyrosinemia

Neurology

X-linked Intellectual Disability, Tuberous Sclerosis, Septo-Optic Dysplasia, Ataxia, Emery-Dreifuss Muscular Dystrophy, Coenzyme q10 Deficiency, Collagen Type VI-Related Disorders, Amyotrophic Lateral Sclerosis, Autism Spectrum Disorders, Holoprosencephaly, Charcot-Marie-Tooth Neuropathy, Macrocephaly/Overgrowth Syndrome, Hereditary motor-sensitive neuropathies, Comprehensive Muscular Dystrophy/Myopathy, Cerebral Cavernous Malformation, Generalized and Focal Epilepsy, Epileptic Encephalopathy, Metabolic Epilepsy, NCL and Progressive Myoclonic Epilepsy, Leukodystrophy and Leukoencephalopathy Panel LGMD and Congenital Muscular Dystrophy, Nemaline Myopathy, Congenital Myasthenic Syndromes, Dementia, Dystonia, Lissencephaly, Polymicrogyria, Neuronal Migration Disorder, Microcephaly and Pontocerebellar Hypoplasia, Parkinson Disease, Periodic Paralysis, Spastic Paraplegia, Spinal Muscular Atrophy, Migraine

Nephrology

Alport Syndrome, Branchio-Oto-Renal (BOR) Syndrome, Bartter Syndrome, Gietelman Syndrome, Salt-losing tubulopathies, Primary Hyperoxaluria, Pseudohypoaldosteronism, Joubert Syndrome, Ciliopathy, Primary Ciliary Dyskinesia, Bardet-Biedl Syndrome, Liddle Syndrome, Hypomagnesemia Nephrolithiasis, Nephronophthisis, Cystic Kidney Disease, Polycystic Kidney Disease, Hypophosphatemic Rickets, Nephrotic Syndrome, Meckel Syndrome, Monogenic Obesity, Diabetes Insipidus, Hemolytic Uremic Syndrome, Renal Malformation (CAKUT), Renal Tubular Acidosis, Senior-Loken Syndrome

Ophthalmology

Retinitis Pigmentosa, Flecked Retina Disorders, Retinal Dystrophy, Congenital Stationary Night Blindness, Leber Congenital Amaurosis, Cone Rod Dystrophy, Corneal Dystrophy, Bardet-Biedl Syndrome, Achromatopsia, Neuro-Ophthalmology Panel, Optic Atrophy, Macular Dystrophy, Albinism,

Joubert Syndrome, Septo-Optic Dysplasia, Stickler Syndrome, Vitreoretinopathy, Usher Syndrome, Ectopia Lentis, Glaucoma, Cataract, Anophthalmia and Anterior Segment Dysgenesis, Microphthalmia, Senior-Loken Syndrome

Pulmonology
Cystic Fibrosis, Cystic Lung Disease, Primary Ciliary Dyskinesia, Bronchiectasis, Central Hypoventilation and Apnea, Hermansky-Pudlak Syndrome, Interstitial Lung Disease Panel Neonatal Respiratory Distress – Surfactant Dysfunction, Pulmonary Artery Hypertension (PAH)

Analysis of cell free DNA:
Fetal, Tumoral, Urinary, Cerebrospinal fluid, Salivary

Whole genome sequencing (WGS) for:
Complex DNA rearrangements

Transcriptome analysis

MicroRNA analysis:
- screening of cardiopathies and tumors