CentoXome® & CentoGenome®

WHOLE EXOME AND WHOLE GENOME ANALYSIS FOR YOUR PATIENTS
We have a life-long dedication to our patients

CENTOGENE is a rare disease company focused on transforming clinical, genetic, and biochemical data into medical solutions for patients. We are dedicated to providing precise medical diagnosis of inherited diseases at the earliest possible moment, and to transforming medical expertise and analytical information into actionable results for physicians, patients, and pharmaceutical partners.
In spearheading the development of genetic testing, we have always balanced diagnostic power with cost-effectiveness across our portfolio.

CENTOGENE offers the broadest genetic testing portfolio for our clinical partners, that is unmatched by anyone else; from individual variant hotspots to the whole genome, and complemented by biomarkers.

The “best test” choice depends on your diagnostic need. We recommend testing as broad as necessary, to cover all aspects suggested by the patient’s phenotype/symptoms.

Our comprehensive CentoXome®, whole exome sequencing (WES), or CentoGenome®, whole genome sequencing (WGS), testing solutions enable you to shorten the diagnostic journey of your patients.

**Innovation for Faster and Better Results**

Pioneers in the diagnosis of rare genetic diseases since 2006

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**INNOVATION FOR RAPID DIAGNOSIS**

- We invest in diagnostic research to increase the diagnostic yield and deliver the most accurate results
- Our reference databases and bioinformatic intelligence are continuously improved

**BENEFIT FROM DEEP INSIGHT**

- We have unique expertise in rare inherited diseases and interpretation of sequencing and biomarker data
- Therefore, we match the highest standard of medical reporting
Accurate diagnosis of rare diseases patients can be difficult. With comprehensive WES and WGS testing, complex and ambiguous cases can often be solved quickly and with high diagnostic yield.\textsuperscript{1-7}

Since 2006, CENTOGENE has been providing genetic testing solutions around the world. We have performed thousands of WGS and tens of thousands of WES tests, constantly helping healthcare professionals to diagnose their patients and make better treatment decisions.

**Where do CentoXome\textsuperscript{®} and CentoGenome\textsuperscript{®} return the highest value?**

It is recommended to choose WES, CentoXome\textsuperscript{®}, or even the more comprehensive WGS, CentoGenome\textsuperscript{®}, when:

- Symptoms are very broad, complex, or unspecific, not pointing towards specific disease or typical phenotype
- Prior focused testing did not provide a conclusive diagnosis

**When to test all genes in one step**

The use of WES and WGS as first-line test rather than a test of last-resort has already been shown to be beneficial for several patients populations.\textsuperscript{1-7} Both tests are returning highest diagnostic value in:

- Complex, heterogeneous neurological diseases
- Unspecific neonatal and pediatric diseases
Genomic testing can lead to a diagnosis in 20–70% of patients suspected to suffer from rare genetic conditions.\(^2,3,5-12\)

**Highest quality for both tests**

Whether you chose CentoXome\(^*\) or CentoGenome\(^*\), we guarantee superior technical, scientific, and medical expertise, reducing diagnostic uncertainties, and supporting patient diagnosis.

- Both tests deliver high diagnostic yields across a variety of molecular etiologies\(^1,13\)
- CentoGenome\(^*\) can provide a diagnosis even in cases where WES did not\(^13\)

<table>
<thead>
<tr>
<th></th>
<th><strong>CentoGenome(^*)</strong></th>
<th><strong>CentoXome(^*)</strong></th>
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<tbody>
<tr>
<td><strong>COVERAGE</strong></td>
<td>~99% of the genome covered at ≥10x</td>
<td>≥98% of targeted regions covered at ≥20x</td>
</tr>
<tr>
<td><strong>GENE REGIONS</strong></td>
<td>Coding (exonic) and non-coding regions (intronic and regulatory regions, and splice sites)</td>
<td>Coding (exonic) regions and exon/intron boundaries</td>
</tr>
<tr>
<td><strong>UNIFORMITY OF SEQUENCING DATA</strong></td>
<td>Highest</td>
<td>High</td>
</tr>
<tr>
<td><strong>TYPES OF PATHOGENIC VARIANTS DETECTED</strong></td>
<td>SNVs, InDels and CNVs(^*)</td>
<td>Yes</td>
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<td></td>
<td>Large and more complex structural variants</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>CLINICAL UTILITY</strong></td>
<td>Diagnostic yield</td>
<td>Highest (reveals also variants not identified by WES)</td>
</tr>
<tr>
<td></td>
<td>Reduction of time-to-diagnosis</td>
<td>Highest (when done as first step)</td>
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<tr>
<td></td>
<td>Value of data for potential future reanalysis</td>
<td>Highest</td>
</tr>
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SNVs: single nucleotide variants
InDels: small insertions and deletions
CNVs: copy number variants; "detection of CNVs is an additional option for all CentoXome\(^*\) tests
Diagnostic Strategies: Balancing Cost & Benefit

Decision factors are diverse when choosing the next step.

When time gives you the luxury of testing choices

WGS can provide superior diagnostic results over those of WES or gene panels,\textsuperscript{2,3,7} however the initial cost is higher. WGS is worth considering because it can often reduce the length of hospital stay or avoid costs of other testing or even wrongly recommended therapies.\textsuperscript{4,6,16,17} However, in the cases the initial cost of WGS’s remains a major barrier, it is still very reasonable to start with WES, or even with a large gene panel.

\textbf{CentoXome\textsuperscript{*}} is the best choice when you need a cost-effective solution for the diagnosis of complex and unsolved cases.

When a rapid diagnosis is crucial

There is not always the time for serial testing strategies that may take too much time when a fast diagnosis is a medical necessity.\textsuperscript{6,8,16,17} In such cases, WGS as a first-line test is the recommended method of choice.

\textbf{CentoGenome\textsuperscript{*}} is the most comprehensive solution to diagnose complex and undiagnosed cases rapidly and with the highest chances of diagnostic success.

When you have a strong diagnostic hypothesis and need a smart solution

NGS Panel Genomic are gene panel tests based on WGS. You chose the panel out of the comprehensive list of CENTOGENE’s well curated gene panels that best suits your patient’s needs or supports your diagnostic hypothesis:

- **STEP 1** - Sequence the whole genome, but initially analyze and report from only the chosen genes.
- **STEP 2** - If the result is negative – upon your request and at an incremental fee - analyze all genomic data, without repeated sampling and sequencing effort.

\textbf{NGS Panel Genomic} is our most flexible and powerful testing product that combines high diagnostic yield with the potential to diagnose at the more affordable initial cost, when compared to a whole genome testing.
Testing Strategies for Challenging Cases
WGS is the fast choice or last resort

Patient with challenging diagnoses and undiagnosed cases

- Heterogeneous phenotypes
- Unclear or atypical clinical symptoms
- Unsuccesful testing history

- Confirmation of clinical hypotheses
- Atypical and rare clinical presentations
- Simple and fast reflex to WGS

WES
Most affordable

CentoXome®

WGS
Most complete and fast

CentoGenome®

NGS Panel Genomic
Most flexible

NEXT

+ 

DIAGNOSIS

- 

DIAGNOSIS

+ 

DIAGNOSIS

REFLEX

- 

DIAGNOSIS

+
Beyond sequencing
CENTOGENE’s data interpretation and medically driven support make the difference

Expertise in genome testing complemented with medical interpretations

- CentoXome® and CentoGenome® always include medical reporting based on our clinical interpretation expertise. We perform additional analyses in case of suspicious or unspecific results.
- A team of highly trained clinical geneticists and scientists interpret the data and cross-checks every medical report.
- Test reports always contain actionable clinical results, recommendations, and follow up options.

Variant classification and monitoring of new insights

- Variant classification by CENTOGENE exceeds ACMG guidelines. Wherever available from our complementary biomarker testing or inhouse data, we validate pathogenicity of variants found.
- All historical high-quality classifications are curated and codified into our data repository CentoMD® - a reference for future diagnostic decisions and classifications. This data repository covers a wide-range of ethnicities and includes also complementary metabolic and proteomic data.
- A life-long commitment to our patients with available reanalysis of genomic data and life-long reclassification of reported variants. If new research or other medical cases suggest a different variant classification and thereby a different medical interpretation, we automatically provide a new medical report via the ordering physician.

Trusted advisory and privacy are our priority

- We are committed protecting our patient’s personal data, adhering to the strictest international guidelines and legislations on data privacy. This includes full compliance to the European GDPR and U.S. HIPAA, in each case where applicable.
- We are a trusted advisor to healthcare professionals, not only for individual patient cases, but also for testing details and strategies.
- If you have any general questions regarding our solutions or received medical reports, our customer support team is readily available to assist you by phone as well as email.
CentoXome® Solo: DIAGNOSIS OF A TREATABLE IMMUNOLOGICAL DISEASE

CentoXome® Solo identified a disease-causing homozygous deletion in a young child with a long-standing history of very early-onset inflammatory bowel disease

**TESTING STRATEGY**
After WES in another lab presented no diagnosis, the physician opted for CentoXome® Solo, due to necessity of diagnosis in determining an effective medication as the patient was not responding to the current therapies

**CLINICAL OVERVIEW**
- 4-year-old female patient with manifestation since 2 weeks old
- Long-standing history of very early-onset inflammatory bowel disease, not responding to current therapies, and presenting recurrent relapses acidosis, periventricular leukomalacia
- Unrelated parents, negative family history

**DIAGNOSIS OF INFLAMMATORY BOWEL DISEASE TYPE 25**
- CentoXome® Solo identified a homozygous, likely pathogenic deletion involving the complete exon 3 of IL10RB
- Disorder: Inflammatory bowel disease type 25, early-onset (OMIM # 612567, autosomal recessive)

**TESTING IMPACT**
- CentoXome® Solo provided a definitive genetic diagnosis, because it was able to identify the causative deletion. This deletion would have been missed by microarrays due to being smaller than the limit of detection and not being detected by the previous WES at another lab
- Bone marrow transplantation offers the only potential cure for this disease, and due to the diagnosis, the patient was eligible for treatment, and the search for a compatible donor started
- The family received genetic counselling
CentoXome® Trio identified a disease-causing homozygous variant in a young child with developmental delay and highly heterogeneous symptoms.

**CLINICAL OVERVIEW**
- 1.5-year-old male
- Global developmental delay, irritability, seizures, status epilepticus, cerebellar vermis hypoplasia, nystagmus, hyperreflexia, metabolic acidosis, periventricular leukomalacia

**TESTING STRATEGY**
Physician sought out CentoXome® Trio, because the patient presented very heterogeneous symptoms related to epilepsy and lack of family history for epilepsy.

**DIAGNOSIS OF PYRIDOXINE-DEPENDENT EPILEPSY**
- CentoXome® identified a homozygous pathogenic variant in \textit{ALDH7A1}
- Inherited from parents, heterozygous carriers
- Disorder: Epilepsy, pyridoxine-dependent (OMIM # 266100, autosomal recessive)

**TESTING IMPACT**
- CentoXome® Trio provided an early and fast genetic diagnosis that would have taken longer by using gene panels, because the symptoms of the child were highly heterogeneous, and many candidate genes could be involved
- Earlier diagnosis triggered treatment with pyridoxine to improve psychomotor development, seizure control and behavior
- The family received genetic counselling
Following negative WES results, CentoGenome® Solo identified compound heterozygous pathogenic variants, one of them being a heterozygous exon deletion.

### CLINICAL OVERVIEW

- 1-year-old male and manifestation since birth
- Developmental delay, delayed motor development, delayed language development, intellectual disability, microcephaly, abnormal skin pigmentation, skin reticularis rash on face and photophobia
- Parents are non-consanguineous, and no other family member affected

### TESTING STRATEGY

The physician opted for CentoGenome® Solo, after WES Trio (in another lab) without diagnosis, due to the severity of the disease and the need to find a diagnosis to guide for intervention.

### DIAGNOSIS OF BLOOM SYNDROME

- CentoGenome® Solo identified two compound heterozygous pathogenic variants in *BLM*
- Carrier testing of the parents confirmed the compound heterozygous state of the variants
- Disorder: Bloom syndrome (OMIM # 210900, autosomal recessive)

### TESTING IMPACT

- CentoGenome® Solo provided a definitive diagnosis because it identified both variants types in the patient. The previous WES at another lab did not detect the deletion
- Due to the diagnosis the patient started symptomatic and preventive measures, such as avoiding exposure to sun and radiation, and a surveillance program for early detection of several types of cancers
- The family received genetic counselling

Het c.3164G>C, p.(Cys1055Ser)
Het deletion covering exons 11 and 12
Compound heterozygous c.3164G>C, p.(Cys1055Ser) and deletion covering exons 11 and 12
CentoGenome® Trio identified a homozygous deep intronic variant, after a negative WES test for Bartter suspicion.

**PATIENT AND CLINICAL PRESENTATION**
- 2-years-old male with clinical suspicion of Bartter syndrome
- Failure to thrive, hypokalemia, hypomagnesemia, and alkalosis
- Consanguineous healthy parents and two more sons affected

**DIAGNOSIS OF GITELMAN SYNDROME**
- CentoGenome® Trio identified homozygous deep intronic variant in SLC12A3
- Inherited from parents, heterozygous carriers
- Disorder: Gitelman syndrome (OMIM # 263800, autosomal recessive)

**TESTING STRATEGY**
The physician opted for CentoGenome® Trio, after multiple evaluations and a negative WES, with the aim of finding a diagnosis and enabling prenatal testing in subsequent pregnancies.

**DIAGNOSIS OF GITELMAN SYNDROME**
- CentoGenome® Trio identified homozygous deep intronic variant in SLC12A3
- Inherited from parents, heterozygous carriers
- Disorder: Gitelman syndrome (OMIM # 263800, autosomal recessive)

**TESTING IMPACT**
- CentoGenome® Trio provided a successful diagnosis of Gitelman syndrome because it covers also the intronic regions; WES is restricted to exons
- Testing with CentoGenome® Trio enabled the identification of the variant; carrier testing for one affected brother also detected the familial variant in a homozygous state
- The family received genetic counselling focused on understanding the risk of recurrence
- The patient and the affected siblings started symptomatic treatment oriented to alleviate common clinical manifestations that are associated with electrolyte abnormalities
The CENTOGENE Advantage
A comprehensive diagnostic solution beyond DNA testing

OUR DIAGNOSTIC SERVICES ARE MORE THAN LABORATORY AND BIOINFORMATICS.

**CentoCard®**
Our dried blood spot collection device makes global sample logistics almost as easy as sending a letter. Collected samples are unaffected by shipping time or temperature, and a single card enables genetic and metabolic testing.

**CentoPortal®**
A user-friendly and fully-secure online service designed to assist in ordering tests, transferring patient data, administering patient’s samples, and accessing your diagnostic reports 24/7.

**Extended Phenotyping**
Structuring your patient’s symptoms into Human Phenotype Ontology (HPO) terms ensures the best quality of clinical information for data interpretation.

**CentoMD®**
The world’s largest mutation database of rare diseases, with over 375,000 analyzed cases and more than 10 million unique variants, supports our medical interpretation.22

**Data safety and research use**
With transparent and easy-to-understand consent forms, your patients can make educated decisions without worrying about data protection. By consenting to the research and storage option, you and your patients will advance research, the understanding of rare diseases, and the quality of future diagnoses and therapies.

**Clinical studies and pharmaceutical partnerships**
By participating in clinical studies, your patients benefit as they foster the development of new therapies and improved monitoring. Through pharmaceutical partnerships, we also leverage our expertise to speed up drug development in rare diseases.

**Multioomics testing**
Continuous research identifies and validates biomarkers, increasing disease understanding and enabling therapy monitoring. This has already added diagnostic certainty to lysosomal storage disorders and other diseases.

**World class expertise**
CENTOGENE’s reputation is built on an international team of genetic and bioinformatics experts, the latest lab technology, continuously improved processes and protocols, and unique data analysis software.
References

1 Bowling et al., 2017; PMID: 28554332
2 Clark et al., 2018; PMID: 30002876
3 Lionel et al., 2018; PMID: 28771251
4 Farnaes et al. 2018; PMID: 29644095
5 Fogel, 2018; PMID: 29325607
6 Soden et al., 2014; PMID: 25473036
7 Stavropoulos et al., 2016; PMID: 28567303
8 Kingsmore et al., 2019; PMID: 31564432
9 Niguidula, et al. 2018; PMID: 30318729
10 Taylor et al., 2015; PMID: 25985138
11 Trujillano et al., 2017; PMID: 27848944
12 Vissers et al. 2017, PMID: 28333917
13 Data on file at CENTOGENE
14 Gilissen et al., 2014; PMID: 24896178
15 Ostrander et al., 2018; PMID: 30109124
16 Petrikin et al., 2018; PMID: 29449963
17 Willig et al., 2015; PMID: 25937001
18 Kalia et al., 2017; PMID: 27854360
19 The European General Data Protection Regulation (GDPR)
20 USA Health Insurance Portability and Accountability Act (HIPAA)
21 Please for details see www.centogene.com/diagnostics/privacy-policy
22 CentoMD® 5.6
We have a life-long dedication to our patients
Your partner of choice

For further information and support, please contact our closest representative or our customer support team, easily accessible by phone or email.

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