CENTOGENE
THE RARE DISEASE COMPANY

CentoXome®
Turning Years Into Days

PRODUCT SHEET

CentoXome®
Whole Exome Sequencing

With more than 7,000 identified rare diseases and approximately 80% being linked to genetic causes, diagnosing rare disease patients can often be difficult – resulting in lengthy, expensive, and emotional diagnostic odysseys.

With Whole Exome Sequencing (WES), you have the genetic testing tool in hand to diagnose your patients in less time with high levels of certainty. CENTOGENE's enhanced WES service – CentoXome®, provides highly uniform coverage of the entire exome and mitochondrial genome, and nearly complete coverage of all known disease-causing regions throughout the genome in a single test. The improved test design includes the most up-to-date scientific knowledge and unique insights based on the world's largest real-world data repository for rare and neurodegenerative diseases, paired with life-long support from the leader and trusted partner in diagnostics. With CentoXome, we help you provide patients with the answers they need today for a better tomorrow.

Have you heard about our newest multiomic add-on? CentoXome MOx — By combining genetic and biochemical testing, we now deliver an even quicker and more accurate diagnosis of rare, metabolic, and neurodegenerative diseases. We are going beyond genetics for a higher diagnostic yield.

The CENTOGENE Advantage

Turn Our Expertise Into Your Advantage
Best-in-class insights powered by the world's largest rare disease-centric Bio / Databank from the leader and trusted partner in rare disease diagnostics

Turn Your Open Questions Into Answers
Superior technology from the experts in omics laboratory testing for rare diseases, combined with outstanding clinical coverage and unmatched diagnostic power in a single test

Turn Our Commitment Into Your Promise
Life-long support by a team dedicated to improving the lives of patients with rare diseases

Outstanding Clinical Coverage and Diagnostic Power

The CentoXome design and service delivers the ideal quality and performance from the world leader and trusted partner in rare disease diagnostics with outstanding clinical coverage and unmatched clinical diagnostic power in a single test. Coupling insights from our rare disease-centric Bio / Databank with superior omics technology, you benefit from a unique approach that increases diagnostic yield by up to 20 % compared to standard WES.[1–9]

Key Features and Performance

BROAD AND UNIFORM EXOME & MITOCHONDRIAL GENOME COVERAGE

- Mean depth ≥ 100 x
- Highly uniform coverage of the entire exome (~ 20,000 genes), +/– 10 bp exon-intron boundaries, and complete mitochondrial genome (37 genes); with ≥ 98.0 % target regions covered at ≥ 20 x

ENHANCED COVERAGE OF CLINICALLY RELEVANT REGIONS

- ~ 8000 disease-associated genes (OMIM®, HGMD®, CENTOGENE's rare disease-centric Bio / Databank), with ≥ 99.0 % target regions covered at ≥ 20 x
- > 99.0 % of all known clinically relevant variants in coding and non-coding regions (HGMD®, ClinVar, CENTOGENE´s rare disease-centric Bio / Databank)

VARIANT TYPES

- Highly sensitive and specific detection of SNVs, InDels, CNVs of exon-level to cytogenomic-level changes, UPD*, and mtDNA with heteroplasmy ≥ 15 %
- Sensitivity
  - SNVs and InDels (≤ 55 bp) > 99.6 %
  - CNVs (≥ 3 exons)** > 95.0 %
- Specificity of > 99.9 % is guaranteed for all reported variants***

TECHNICAL DETAILS

- Illumina paired-end next-generation sequencing (NGS) technology (2 x 150 bp)
- Exome capture with custom-designed reagents based on Twist® Human Core Exome, with 18 – 20 Gb of sequencing data generated per patient
- Nuclear genome aligned to GRCh37 / hg19 Human genome assembly
- Mitochondrial genome aligned to Cambridge Reference Sequence of the Human Mitochondrial DNA (NC_012920)

SNVs: single nucleotide variants; InDels: small insertions / deletions; CNVs: copy number variations; UPD: uniparental disomy; mtDNA: mitochondrial DNA

* UPD screening is performed using an in-house specific algorithm for the following well-known clinically relevant chromosomal regions: 6q24, 7, 11p15.5, 14q32, 15q11q13, 20q13 and 20

** CNV detection software has a sensitivity > 95.0 % for all homozygous / hemizygous and mitochondrial deletions, as well as heterozygous deletions / duplications and homozygous / hemizygous duplications spanning at least three consecutive exons

*** Variants with low quality and / or unclear zygosity are confirmed by orthogonal methods (i.e., SNVs and InDels by Sanger sequencing; CNVs by Multiplex ligation-dependent probe amplification, MLPA; quantitative polymerase chain reaction, qPCR; or chromosomal microarray, CMA)

Tailored Testing and Life-Long Diagnostic Support

We offer flexible testing options and additional services to provide a CentoXome analysis tailored to your patient's needs, such as WES for ongoing pregnancies with fetal abnormalities for prenatal diagnostics, CentoXome Prenatal, and a multiomic WES solution, CentoXome MOx, that integrates deep exomic and biochemical insights in a single test, enabling early diagnosis, better prognosis, and optimized treatments for rare and metabolic diseases. Committed to improving the lives of patients, our CentoXome testing solutions are paired with life-long diagnostic support via a free-of-charge and proactive reclassification program, as well as an affordable case-level reanalysis.

Options & Additional Services

TURNAROUND TIME	• Regular: ≤ 30 business days • FAST: ≤ 15 business days
TESTING DESIGN	Solo, Duo, Trio, and Trio PLUS*
RAW DATA	Raw data available free-of-charge for download (FASTQ, BAM, VCF files) along with filtered and annotated variant table (XLS file) for further research
GENOME-WIDE ANALYSIS OF STRUCTURAL VARIANTS	Genome-wide high-resolution analysis of SVs / large CNVs through CentoArray (CMA)
LIFE-LONG RECLASSIFICATION AND RE-ANALYSIS	• Proactive variant-level re-evaluation and reclassification at no extra cost** • Case-level reanalysis and medical reinterpretation at an affordable cost in case of uncertain or negative results (i.e., new clinical information, one-year intervals)
CENTOXOME PRENATAL*	• Expedited and prioritized testing (≤ 15 business days) specifically designed for ongoing pregnancies • Includes cell culture and maternal contamination testing
CENTOXOME MOX	• Integrates WES with biochemical testing for inherited metabolic disorders (IMDs) and hereditary angioedema (HAE), including proprietary biomarkers, in a single solution • Biochemical testing allows for orthogonal confirmation of disease accelerating the diagnosis path by avoiding stepwise testing • Indicated for patients with complex and overlapping symptoms, varying age of onset and severity, or symptoms suggestive of IMDs or HAE (e.g., babies and children critically ill that need a fast diagnosis, babies with abnormal newborn screening results, patients with symptoms related to neurological conditions of unknown etiology)

We are ready to go beyond genetics, to go beyond diagnostics. Learn now more about our Multiomic Solutions: centogene.com/mox

Solo: only the affected index patient is tested; Duo: index patient and affected or unaffected family member are tested; Trio: index patient and two family members, affected or unaffected are tested; PLUS: additional family member beyond Trio is tested
SVs: structural variants; CNVs: copy number variants; sWGS, shallow whole genome sequencing; CMA: chromosomal microarray analysis

* Mitochondrial genome analysis is performed only for the index patient and maternal samples
** We do not offer WES-based CNV and mitochondrial genome analysis with CentoXome Prenatal due to technical limitation. More details about Prenatal Testing
*** More details about Variant Reclassification Program

Best-in-Class Medical Reporting and Extra Insights

When choosing our WES services, patients, physicians, and partners can feel confident that they will receive high-quality sequencing combined with best data analysis and interpretation, documented in comprehensive medical reports. By combining deep phenotype data with genotype data using our advanced bioinformatic pipeline and artificial intelligence, CENTOGENE accurately identifies and prioritizes disease-causing variants to deliver best-in-class clinical interpretation and reporting. A team of highly trained clinical geneticists and scientists interpret the data and cross-check every medical report. We perform additional testing and use our Bio/Databank data to confirm results and validate variant pathogenicity.

Medical Reports and Extra Expertise Insights

MAIN FINDINGS	• Diagnostic findings related to patients' phenotype • Research findings related to patients' phenotype providing information on potential diagnoses in cases where no definitive diagnosis can be found
SECONDARY FINDINGS	• Optional findings unrelated to patients' phenotype • Medically actionable variants based on the American College of Medical Genetics and Genomics (ACMG) guidelines available for all tested individuals
POTENTIAL RELEVANT FINDINGS	• Findings unrelated to patients' phenotype that might be clinically relevant to help close diagnostic gaps • List of variants for the index patient related to disorders without an apparent overlap with the described phenotype and/or variants with a zygosity inconsistent with the expected mode of inheritance
CARRIERSHIP FINDINGS	• Optional carriership status findings not related to patients' phenotype that are potentially clinically relevant for family planning • List of sequence variants for the index patient classified as pathogenic/likely pathogenic in our Bio/Databank for selected genes associated with recessive severe and early-onset Mendelian diseases
EXTRA INSIGHTS	Extra insights supported by our Bio/Databank, which contains curated unique variants and omics data from a wide range of ethnicities from more than 120 countries, are used to confirm results and validate pathogenicity of the variants found.

More details about Medical Reporting at CENTOGENE and Carriership findings reported in WGS and WES.
Please note that for prenatal diagnostics research, secondary and additional carriership are not reported.

References
[1] Cheema et al. 2020, PMID: 3308301
[2] Clark et al. 2018, PMID: 30002876
[3] Gross et al. 2018, PMID: 30293986
[4] Posey et al. 2019, PMID: 31234920
[5] Schon et al. 2020, PMID: 3267494
[6] Scuffins et al. 2021, PMID: 33495530
[7] Stark et al. 2016, PMID: 26938784
[8] Trujillano et al. 2017, PMID: 27848944
[9] Wagner et al. 2019, PMID: 31059585