CENTOGENE
THE RARE DISEASE COMPANY

NEW CentoXome®
TURNING YEARS INTO DAYS

PRODUCT SHEET

NEW 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 the highest levels of certainty. CENTOGENE's newly enhanced WES service – NEW CentoXome®, provides highly uniform coverage of the entire exome and mitochondrial genome, and almost full coverage of all known disease-causing regions throught 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 rare-disease centric Bio/Databank in rare diseases, paired with life-long support from the leader & trusted partner in diagnostics. With NEW CentoXome, we help you provide patients with the answers they need today for a better tomorrow.

The CENTOGENE Advantage

Turn Our Expertise Into Your Advantage
Best-in-class insights powered by the world's largest rare disease-centric Bio/Databank in rare diseases 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 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 NEW CentoXome design and service delivers the ideal quality and performance from the world leader and trusted partner in rare diseases diagnostics with outstanding clinical coverage and unmatched clinical diagnostic power in a single test. Coupling insights from our extensive Bio/Databank in rare diseases with superior omics technology, patients and physicians benefit from a unique approach that increases diagnostic yield by up to 20 % compared to routine WES[1–9] via enhanced coverage of the exome, full mitochondrial genome, and known medically-associated genes and variants in the exome and non-coding region.

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) and mitochondrial genome (37 genes); ≥ 98.0 % target regions covered at ≥ 20 x
- All protein coding regions of nuclear genes, +/- 10 bp exon-intron boundaries, and complete mitochondrial genome

ENHANCED COVERAGE OF MEDICALLY RELEVANT REGIONS

- ~ 8000 disease-associated genes (OMIN®, HGMD®, CENTOGENE), with ≥ 99.5 % target regions covered at ≥ 20 x
- > 99 % of all known clinically relevant variants in coding and non-coding regions (HGMD®, ClinVar, and CENTOGENE's Bio / Databank for rare diseases)

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 NGS technology (NovaSeqTM 6000 sequencing system, 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: variants in 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, MPLA; 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 NEW CentoXome analysis tailored to your patient's needs, such as WES for ongoing pregnancies with fetal abnormalities for prenatal diagnostics and expedited WES for critically ill patients that need rapid and precise genetic diagnosis. Committed to improving the lives of patients with rare diseases, NEW CentoXome is 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*
PRENATAL TESTING*	Expedited and prioritized testing (≤ 15 business days) specifically designed for ongoing pregnancies; includes cell culture and maternal contamination testing
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
ANALYSIS OF LARGE DELETION/DUPLICATIONS	Genome-wide high-resolution analysis of SVs / large CNVs through CentoLCV (sWGS) and CentoArrayCyto® 750K or HD (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)

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
* More details at Prenatal Testing
** More details at 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 high-quality 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 • Optional research findings related to patients' phenotype providing information on potential diagnoses in cases where no definitive diagnosis can be found
OPTIONAL SECONDARY FINDINGS	Medically actionable variants based on American College of Medical Genetics and Genomics (ACMG) guidelines available for all tested individuals
ADDITIONAL FINDINGS	CENTOGENE's "Tabular List" variant section for the index patient, which includes known gene variants in our Bio/Databank classified as pathogenic / likely pathogenic. Our list makes often unreachable information accessible to physicians/genetic counselors, which may lead to further diagnostics and medical management of the patient and/or their family
COMPLEMENTARY TESTING & EXTRA INSIGHTS	• Complementary testing is performed to confirm results and validate variants pathogenicity as necessary and when available from our complementary omics testing platform (e.g., enzyme activity, biomarker quantification) • Extra insights supported by our Bio/Databank, which contains curated unique variant data 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 at Medical Reporting at CENTOGENE and CENTOGENE's 'Tabular List' Variant Section.

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