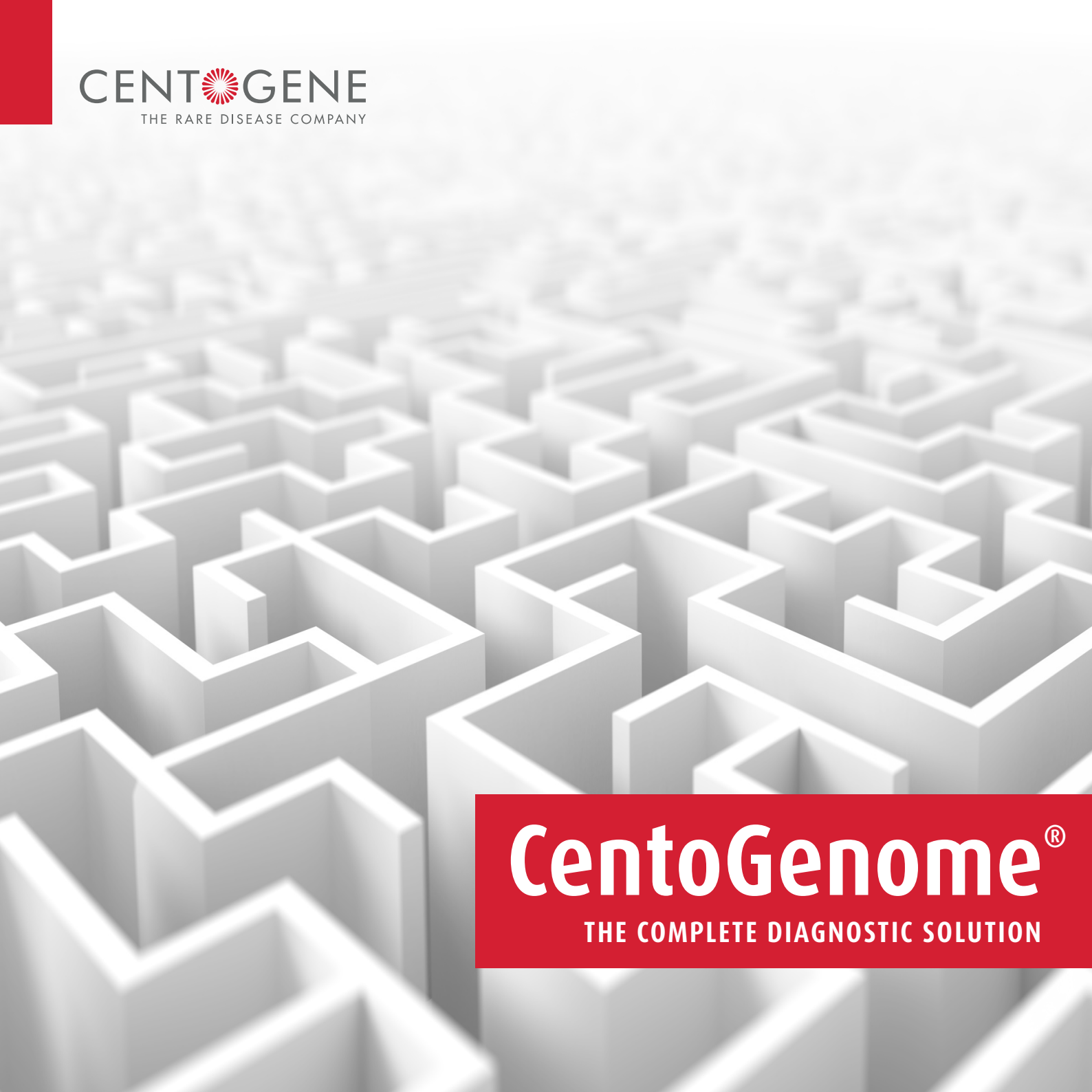
CENTOGENE

THE RARE DISEASE COMPANY



CentoGenome®

THE COMPLETE DIAGNOSTIC SOLUTION

Often, after months, years and many costly tests, patients and physicians find themselves back where they started – sometimes with a dramatic deterioration of patients' quality of life.

Now you can escape the maze with a single test – one which provides a comprehensive view into genetic information paired with highest quality of medical interpretation.

Introducing the diagnostic solution

CENTOGENE is revolutionizing genetic diagnostics with CentoGenome® – our premium whole genome analysis service for the diagnosis of complex diseases.

Whole genome sequencing (WGS) with CentoGenome® provides the most comprehensive genetic testing available for the diagnosis of rare diseases. It identifies a broader range of DNA sequence variation and offers greater sensitivity than any other technology available.
Together with CENTOGENE's proprietary mutation database (CentoMD®) and the highest level of medical interpretation and reporting, CentoGenome® provides definite answers for patients with unresolved diagnoses.

CentoGenome® offers

- **SENSITIVE ANALYSIS**
  unparalleled genome coverage and multi-variant detection
- **RELIABLE INTERPRETATION**
  proven success from over 10 years of medical-focused diagnostic work
- **FAST RESULTS**
  guaranteed rapid turnaround times through optimized workflows
- **ACCESSIBLE LOGISTICS**
  easy and cost effective transfer of specimens on CE-IVD labeled CentoCard® without compromising the sample integrity
- **AFFORDABLE PRICING**
  high throughput HiSeqX platform allows lowest production cost for whole genomes sequencing

Why whole genome sequencing?

WGS identifies nearly all changes in a patient's DNA by sequencing the entire coding and non-coding regions of the genome. It provides detailed information on the thousands of genes involved in normal growth and development and of all the 'silent' genomic regions simultaneously. Existing research and diagnosis of genetic diseases have been heavily biased towards mutations in gene coding regions, that represents only 1% of a patient's entire genome. Numerous clinical studies now exist which reveal the critical role of non-coding sequence variants in diseases.

ALL GENETIC TESTS IN ONE

Single variant testing, panel testing and microarrays all identify known variants in pre-determined genes, and whole exome sequencing (WES) analyses only regions that encode functional proteins. Although in many cases these tests are sufficient to identify the cause of a disease, these analyses have inherent limitations and can fail to reveal the full genetic cause.

Millions of patients today suffer from wrongly or undiagnosed genetic diseases because the most suitable technology was not applied. WGS offers comprehensive identification of many more variants simultaneously in a single assay.

BETTER SENSITIVITY IN CODING AND NON-CODING REGIONS

WGS captures nearly complete information on a patient's genetic constitution, far better than WES across both the gene coding or non-coding regions. This implies that WGS captures more variants, few of which are causative of disease development and progression, gives a more complete picture of the genetic landscape for a precise diagnosis and in many cases information also on precise treatment options.

In a recent study[1], next-generation sequencing for WGS and WES both identified the vast majority of single nucleotide variations (SNVs) and insertions/deletions (indels), but WES missed about 3% potential 'high-quality' variants, demonstrating that WGS is more powerful than WES for detecting potential disease-causing mutations even within exonic regions. The study concluded that "*compared to WES, only WGS is able to provide hitherto unprecedented complete coverage of the coding region of the genome.*"

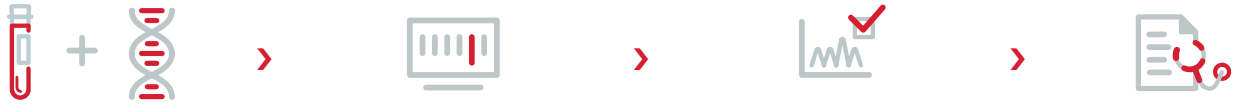
[1] Meienberg J et al. Clinical sequencing: is WGS the better WES? Hum Genet. (2016)

CentoGenome: whole genome sequencing and analysis at CENTOGENE

Centogene performs whole genome sequencing in the index patient as well as in two family members (TRIO); or in affected relatives to provide the most complete diagnostic solution.

A comprehensive view on genetic information paired with conclusive medical interpretation

The large amount of data generated by WGS requires filtering and verification to accurately identify high-quality candidate variants and pinpoint the correct one, a skill that few variant physicians or analysts possess. This is where Centogene provides exceptional assistance, with its proprietary database (CentoMD®) and it's expert analysis team backed by thousands of WES/WGS analyses and assessments done within its clinical setting.



SEQUENCING OF THE GENOME*

END-TO-END BIOINFORMATICS ANALYSIS OF RAW DATA

VALIDATION OF SEQUENCING RESULTS

MEDICAL REPORTS

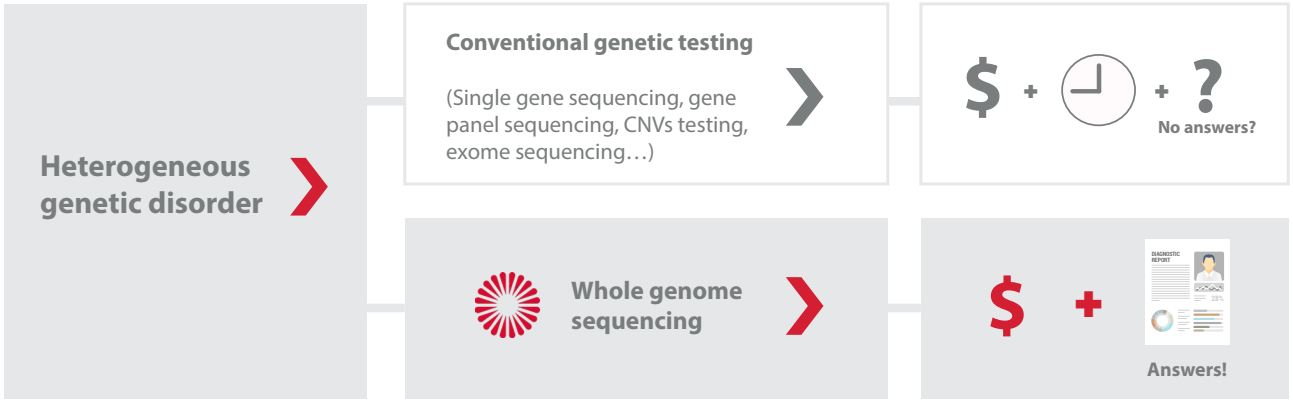
* mean coverage of 30x (>98% of the genome is covered at >10x)

Our genome pipeline includes all of the following in a single, in-house workflow:

- In-house validated sequencing workflow of all coding and non-coding genomic regions utilizing Illumina next generation sequencing (NGS) platform
- Filtering, analysis and interpretation of single-nucleotide variants (SNVs), indels, structural variants and CNVs
- End-to end bioinformatics analysis of raw data with clinical reporting
- Streamlined processes

Key benefits of whole genome sequencing

- CentoGenome® produces a more comprehensive dataset for known human mutations in exons, introns and regulatory regions (Promoter, 5' and 3' untranslated regions)
- CentoGenome® detects CNVs, translocations, splice site variants, regulatory region variants and insertions/deletions, to help interpret their downstream effects in coding regions
- CentoGenome® outperforms WES not only in terms of coverage over the WES targeted exonic regions but also with respect to non-coding regions not captured by WES
- CentoGenome® employs PCR-free approach and hence shows fewer artefacts than WES
- CentoGenome® keeps abreast of the growing clinical knowledge. Over time as the understanding of disorders, genes and variants grows, a simple revisiting of the data updates your previous findings to the latest information in the field, thereby reducing cost and time invested in repeat testing



Key applications of CentoGenome®

Our experts highly recommend the use of CentoGenome® for diagnosis when the patient presents:

- Complex and heterogenous syndromes with an unclear or atypical phenotype
- A phenotype with significant genetic heterogeneity, where mutations in several genes may lead to the same clinical presentation (for example neuropathies, ataxias, intellectual disability, and muscular disorders)
- Causative cancer mutation in tumors at every stage of treatment

Key features of CentoGenome®

● Provided as a part of analysis ○ Provided upon request – Not incuded as a part of analysis		Raw data fastq file	Bioinformatics bam, vcf files	Bioinformatics with annotated and filtered variant report (filtered variant report as Excel table)	Variant validation and comprehensive medical report	Prenatal analysis offered*	TAT (working days)
CentoGenome® (~98% of the genome is covered at >10x at a mean coverage of 30x)	**Solo - Extended**	●	●	–	–	–	< 20
	Solo - Variants	●	●	●	–	–	< 20
	Solo - Advanced	○	○	○	●	–	< 20
	Solo - Advanced with Mitochondrial Genome	○	○	○	●	–	< 20
	Trio - Advanced	○	○	○	●	–	< 20
	Trio - Advanced Fast	○	○	○	●	●	< 12
	Trio - Advanced Plus (each additional family member sequencing beyond Trio)	○	○	○	●	●	< 20
	Trio - Advanced with Mitochondrial Genome	○	○	○	●	–	< 20
CentoGenome® Somatic***	**Basic** (90x tumor/30x normal)	●	–	–	–	–	< 20
	Advanced (90x tumor/30x normal)	○	○	○	●	–	< 25
	Advanced Fast (90x tumor/30x normal)	○	○	○	●	–	< 12
	Deep (140x tumor / 40x normal)	○	○	○	●	–	< 25

* Prenatal testing is currently not offered in the US. Please contact us directly.
** Prenatal testing with a turnaround time of <12 business days.
*** Available soon.

CentoGenome® - for detection of variants in intellectual disability

Role of whole genome sequencing for detection of variants in intellectual disability

Intellectual disability (ID), also referred to as mental retardation, occurs in ~0.5% of newborns and is closely connected to a genetic cause; 15% are due to chromosomal abnormalities, 10% are due to microdeletions, and 10% in males are due to monogenetic alterations[2,3]. The likelihood of a genetic cause for ID in a patient increases with severity of the symptoms.

A detailed clinical analysis with comprehensive genetic testing is known to be the best way to achieve a diagnosis in this disorder, which often has a high level of genetic heterogeneity. WGS analysis with CentoGenome® can be applied as a primary analysis needed to reliably identify and characterize the comprehensive spectrum of genetic variation and provide a genetic diagnosis in the majority of patients with ID.

Microarray and WES studies have shown the prevalence of de novo copy number variations and SNVs in ID, but are not able to diagnose majority of cases that come to the clinic. A recent paper published in Genomic Medicine revealed that WGS analyses of pediatric populations have shown identification of clinically relevant variants in ~40% of those with autism and ~60% of those with intellectual disability[4].

Another scientific group showed that out of a cohort of 170 individuals (85 quartet families), 69.4% carried different ASD-relevant mutations. Whole genome sequencing was applied to analyze de novo and rare inherited single-nucleotide and structural variations that were previously connected with ASD or other neurodevelopmental disorders[5].

WGS analysis provided a conclusive diagnosis in 42% of the 50 patients where array-CGH and WES failed to provide a diagnosis. This demonstrates the precedence of WGS in diagnosing genetically complex disorders. The superiority of WGS sequencing is further supported by other studies where whole genome sequencing could identify the causes of severe intellectual disability[6].

A simple workflow to comprehensively identify different pathogenic variants results in increased diagnostic yield for cases with intellectual disability and hence supports CentoGenome® as the first tier diagnosis for ID, providing the best way to identify variants with expert interpretation and reporting in one complete package.

[2] Vissers et al. Genetic studies in intellectual disability and related disorders. Nat Rev Genet. (2016)
[3] Homberg et al. Genetic and environmental modulation of neurodevelopmental disorders: Translational insights from labs to beds. Brain Res Bull. (2016)
[4] Stavropoulos et al. Whole genome sequencing expands diagnostic utility and improves clinical management in paediatric medicine. Genomic Medicine (2016)
[5] Yuen et al. Whole-genome sequencing of quartet families with autism spectrum disorder. Nat Rev Genet. (2015)
[6] Gilissen et al. Genome sequencing identifies major causes of severe intellectual disability. Nature (2014)

CentoGenome® - for detection of somatic variants in cancer

The genetics underlying any given cancer can be complex and highly individual, involving a number of genes in coding and non-coding regions, in both germline and somatic cells. CentoGenome® is the state-of-the-art technology for identifying variants to guide diagnosis and treatment of somatic cancers.

Somatic mutations are found exclusively in tumor cell genomes; their frequency varies across different cancer types as do the relative proportions of non-coding and coding variants. A high proportion of somatic variants in tumors are structural variants including large genomic rearrangements. Somatic mutations in tumors often fall within known driver genes and hotspots but virtually all solid tumors have additional mutations which have an effect outside the known hotspot region.

A recent review in Nature Genetics[7] compares the genetics of germline versus somatic cancers and highlights the importance of non-coding variants in somatic cancer.

Only WGS is capable of comprehensive tumor profiling across the genome, making it the best option for detecting causative cancer mutation in tumors at every stage of treatment.

TRACKING TUMOUR PROGRESSION

Any changes within the tumor genome can be carefully monitored with CentoGenome®. Consequently, de novo somatic mutations that occur in response to tumor therapy can be identified and treatment modified accordingly. Analysis includes tumor plus normal tissue pair-analysis for a state-of-the-art cancer monitoring.

In somatic cancer investigations, identifying the causative mutations with WGS can be difficult and success relies on specialist expertise in variant filtering as well as access to a broad variant database; CentoGenome® incorporates all of this, enabling you to provide precision medicine treatments for your patient.

[7] Khurana et al. Role of non-coding sequence variants in cancer. Nat Rev Genet. (2016)

CentoGenome® - pioneering WGS data interpretation

CentoGenome® enhances state-of-the-art WGS technology with expert filtering and interpretation of data by experienced professionals with reference to CENTOGENE's comprehensive disease-linked mutation database (CentoMD®).

CONCLUSIVE CLINICAL REPORTS:

- Validated by certified human genetic consultants and geneticists
- Detailed descriptions and explanations of the applied testing methods
- Differential diagnosis and detailed assessment of the clinical information received
- Clear results, recommendations and genetic consultations with clinicians

CLINICAL ANAMNESIS

High quality interpretation of the data requires specific and detailed clinical information from the index patient and the family (TRIO) when performing whole genome sequencing. This increases the diagnostic yield from roughly 20% to over 40%.

INCIDENTAL FINDINGS

CENTOGENE does not report on findings not directly related to the cause of a disease and not listed in the ACMG guidelines (Kalia et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics, Genet Med. (2017).

Please visit our website
for more information:

www.centogene.com

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