CENTOGENE
THE RARE DISEASE COMPANY

MOx 2.0

Multiomic Portfolio

MOx

Beyond Diagnostics.

Why Choose Multiomic Testing

Now Including **RNA-Seq**

Integrated genomic, transcriptomic, and biochemical testing facilitates the decision on the pathogenicity of clinical variants. This approach increases diagnostic yield and reduces the uncertainty. Variants of Uncertain Significance (VUS) are prevalent in genetic diagnostics and create a significant burden by hindering diagnosis and clinical management.

CENTOGENE's multiomic approach integrates multiple data sets (omics) into a single test. In leveraging the most holistic insights, multiomics is a unique and highly effective tool for precise diagnosis of rare and neurodegenerative diseases. The uncertainty of a reported VUS is eliminated by evaluating additional omic data – confirming or negating any effect and empowering physicians to provide timely interventions and personalized treatments. A multiomic approach ultimately improves patient outcomes and alleviates the burdens of prolonged diagnostic odysseys.

MOx

Who Should Consider Multiomic Testing?

Physicians providing a diagnosis and treatment for patients matching any of the following criteria:

- Suspicion of rare diseases, Inherited Metabolic Disorders (IMDs), or neugenerative diseases
- Unspecific symptoms with broad differential diagnosis
- Complex, overlapping symptoms with broad differential diagnosis
- Patients with prior unsuccessful testing history

CENTOGENE's Multiomic Portfolio

CentoGenome MOx 2.0

WGS | Biochemical Testing | RNA-Seq

Whole Genome Sequencing (WGS) according to the specifications of postnatal CentoGenome. RNA-seq evaluates the impact of potential splicing variants. For identified variants, additional metabolic biomarker measurements and enzyme activity testing are performed according to the automated reflex step for available analytes.

CentoXome MOx 2.0

WES | Biochemical Testing | RNA-Seq

Whole Exome Sequencing (WES) according to the specifications of postnatal CentoXome. RNA-seq evaluates the impact of potential splicing variants. For identified variants, additional metabolic biomarker measurements and enzyme activity testing are performed according to the automated reflex step for available analytes.

Specimen Requirements
CentoCard®

Please Note
To achieve proper RNA quality samples are only processed if sample collection date and sample arrival date is within 7 or less days.

CentoGenome MOx 1.0

WGS | Biochemical Testing

WGS according to the specifications of postnatal CentoGenome. For identified variants, additional enzyme activity testing and metabolic biomarker measurements are performed according to the automated reflex step for available analytes.

CentoXome MOx 1.0

WES | Biochemical Testing

WES according to the specifications of postnatal CentoXome. For identified variants, additional enzyme activity testing and metabolic biomarker measurements are performed according to the automated reflex step for available analytes.

Specimen Requirements
CentoCard® or 2 ml EDTA blood

CentoMetabolic MOx

NGS Panel | Biochemical Testing

A panel designed to target the 180 most common IMDs. For identified variants, additional enzyme activity testing and metabolic biomarker measurements are performed according to the automated reflex step for available analytes.

Order a Multiomic Test on Our Online Ordering Portal

Raw and processed data of WES or WGS are available for download without charge for a period of 30-days via CentoPortal.

Multiomic Testing: Genomics, Transcriptomics, and Biochemical Testing

MOx unleashes the potential to improve health outcomes and accelerate the development of treatments by providing the most holistic view of biological systems, disease mechanisms, and personalized medicine applications.

Genomics

CentoGenome (WGS)

Our WGS covers deep intronic and splicing regions and includes comprehensive genomic analysis (e.g., SV, repeat expansion), capturing >7,000 rare diseases, including >1,400 IMDs.

WGS features: Sequence variants, CNVs, mtDNA analysis, uniparental Disomy, repeat expansions, *SMN1* screening, *GBA* conversion screening

CentoXome (WES)

Our WES turns the evaluation of genetic variants into a clear understanding of disease-causing variants in >7,000 rare diseases, including >1,400 IMDs.

WES features: Sequence variants, CNVs, selected intronic variants, mtDNA analysis, uniparental Disomy

Transcriptomics

RNA-seq technology allows us to qualify the impact of potential splicing variants as changes in the composition of genetic information in our medical interpretation. For this purpose, variants in blood expressed genes that could impact splicing are analyzed and functionally evaluated in the RNA data. Our medical experts use this information in combination with the clinical picture of the patient to provide an advanced and more precise variant classification. Our RNA-seq can elucidate undiagnosed genetic diseases and clarify the impact of VUS.

Biochemical Testing

Enzyme activity testing and metabolic biomarker measurement by Tandem-Mass Spectrometry designed to support the diagnosis of rare disease metabolic disorders. In addition, our biochemical portfolio allows cost-efficient screening approaches and disease monitoring.

Biomarkers and Enzymes Included in Multiomic Portfolio

In the multiomic testing environment, biochemical testing evaluates the impact of potentially clinically relevant variants (VUS, LP, P) in genes for the following analytes.

Biomarkers

Gaucher disease
Glucosylsphingosine (lyso-Gb1)*

Fabry disease
Lyso-ceramide trihexoside (lyso-Gb3)

Niemann-Pick disease type A / B / C
Lyso-SM-509

Aromatic L-amino acid decarboxylase (AADC) deficiency
3-O-methyldopa (3-OMD)

Enzymes

Neuronal Ceroid Lipofuscinosis

Santavuori-Haltia disease
Palmitoyl-protein- thioesterase

Jansky-Bielschowsky disease
Tripeptidyl-peptidase

Enzymes

Oligosaccharidoses and Sphingolipidoses

Wolman disease
Acid lipase

Pompe disease
Alpha-glucosidase

Fucosidosis
Alpha-fucosidase

Fabry disease
Alpha-galactosidase

Schindler / Kanzaki disease
Alpha-N-acetylgalactosaminidase

Gaucher disease
Beta-glucocerebrosidase

Tay-Sachs disease
Beta-hexosaminidase

Beta-mannosidosis
Beta-mannosidase

Sandhoff disease
Total-hexosaminidase

Enzymes

Mucopolysaccharidosis

Hurler syndrome (MPS I)
Alpha-L-iduronidase

Hunter syndrome (MPS II)
Iduronate-2-sulfatase

Sanfilippo syndrome B (MPS III B)
Alpha-N-acetylglucosaminidase

Morquio syndrome B (MPS IV B)
Beta-galactosidase

Maroteaux-Lamy syndrome (MPS VI)
Arylsulfatase B

Sly syndrome (MPS VII)
Beta-glucuronidase

* A method using Lyso-Gb1 is covered by US Patent No.10,859,580, other pending US applications, and pending applications and patents in other jurisdictions

Clinical Utility

Beyond Genomics: Using RNA-seq from filter cards to unlock the clinical relevance of non-coding variation in splicing

Clinical WES and WGS are first-line diagnostic methods in rare diseases with diagnostic yields going up to 60 %. Still Variants of Unknown Significance (VUS) account for up to 5 % of reported variations in the ClinVar database.

We identified a total of 108 consecutive patients with 113 splicing variants reported after WES or WGS. In addition, RNA-seq was performed using dried blood spots (CentoCard®). Results showed 49 variants located at canonical intronic positions 1–2 (43 %) and 64 (57 %) affecting other intronic regions (up to 824 bps). Of the 113 variants, 66 (58 %) were confirmed as leading to abnormal splicing, 15 (13 %) did not have any evident splicing effect, and 33 (29 %) were inconclusive (Figure 1).

We propose a method for a systematic experimental evaluation of the splicing impact of intronic variants, integrated in diagnostic WES / WGS, which impact the assessment of their clinical relevance. The approach can be implemented in the workflow of routine diagnostics, adding an additional -omics layer to the diagnosis of rare diseases.

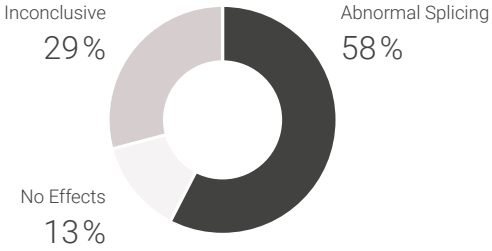

Figure 1: Results of splicing assessment of variants using RNASeq

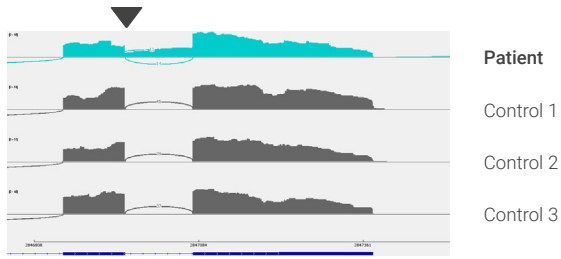

Figure 2: Splicing variant at NM_022575.3:c. 2375+1G>T, Intron 23 *VPS16* gene

Bertoli-Avella et al. 2023

Dive Deeper
in the RNA-Seq
Poster

Clinical Utility

CentoMetabolic MOx: An integrated multiomic approach as an excellent tool for the diagnosis of metabolic diseases

To present our experience using a multiomic approach, which integrates genetic and biochemical testing as a first-line diagnostic tool for patients with IMDs. A cohort of 3,720 patients from 62 countries was tested using a panel including 206 genes with Single Nucleotide and Copy Number Variant (SNV/CNV) detection, followed by semi-automatic variant filtering and reflex biochemical testing (25 assays). In 1,389 patients (37%), a genetic diagnosis was achieved.

Within this cohort, the highest diagnostic yield was obtained for patients from Asia (57.5%, mainly from Pakistan). Overall, 701 pathogenic/likely pathogenic unique SNVs and 40 CNVs were identified. In 620 patients, the result of the biochemical tests guided variant classification and reporting. Top five diagnosed diseases were: Gaucher disease, Niemann-Pick disease type A/B, phenylketonuria, mucopolysaccharidosis type I, and Wilson disease. We show that integrated genetic and biochemical testing facilitated the decision on clinical relevance of the variants and led to a high diagnostic yield (37%), which is comparable to WES/WGS. More importantly, up to 43% of these patients (n = 610) could benefit from medical treatments (e.g., enzyme replacement therapy). This multiomic approach constitutes a unique and highly effective tool for the genetic diagnosis of IMDs.

Almeida et al. 2022

Dive Deeper
in the Metabolic
Publication

MOx

How Does MOx Accelerate Rare Disease Diagnoses?

MOx is a single test solution integrating WES or WGS with biochemical testing for IMDs and RNA-seq for splicing variants. Reducing the burden of Variants of Uncertain Significance (VUS). RNA analyses improve the understanding of splicing impact and provides an advanced and more precise variant classification. Biomarkers serve as measurable indicators of pathological processes. **This critical information helps clinicians and geneticists in determining the pathogenicity of these variants and making more informed clinical decisions.**

For More Information
centogene.com

For Ordering
centoportal.com

CENTOGENE GmbH
Am Strande 7
18055 Rostock
Germany

CENTOGENE GmbH is a subsidiary of CENTOGENE N.V.

Global Partner Support
customer.support@centogene.com
+49 381 80 113-416

For US Partners
customer.support-us@centogene.com
+1 (617) 580-2102

Explore More About Multiomic Solutions at CENTOGENE

Rostock - CLIA #99D2049715

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