CENTOGENE
THE RARE DISEASE COMPANY

# CentoMetabolic®

More Answers Today.
More Options Tomorrow.

PRODUCT SHEET

# CentoMetabolic®

Inherited metabolic disorders (IMDs) are a group of rare conditions caused by genetic defects that disrupt the cellular metabolism. A growing number of IMDs are treatable if diagnosed early, but can be quickly fatal without prompt identification. With a multiomic approach, we can help you and your patients to accelerate the critical journey from symptoms to diagnosis by avoiding stepwise testing – saving time, resources, and pivotal years amid often rapid IMD progression.

CENTOGENE's multiomic panel – CentoMetabolic® – has been designed to test for a wide range of IMDs – integrating genetic and biochemical testing, including enzyme assays as well as a selection of proprietary biomarkers. When genetic variants relevant to your patient are detected via CentoMetabolic, we will automatically complement the analysis with biomarker and/or enzyme testing (if applicable) and include the results in your medical report. In addition, CentoMetabolic includes an evaluation of copy number variants (CNV) at no extra cost. CentoMetabolic gives you the confidence of a complete clinical picture, while laying the roadmap to personalized treatment options.

## The CENTOGENE Advantage

- Curated to **provide the most valuable information** for diagnostic decisions, prognosis, and therapeutic approaches
- The most **up-to-date panel gene content** including the latest medical and in-house findings
- **World-class expertise** and life-long commitment to our patients
- **High-quality analysis for precise clinical interpretation** using advanced bioinformatics and artificial intelligence-powered tools
- **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

# Who Should Consider CentoMetabolic?

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

- Suspected metabolic disorder
- Babies with lethargy or abdominal pain or vomitting or jaundice or metabolic acidosis
- Developmental delay
- Admission to a neonatal intensive care unit (NICU), especially due to epilepsy of unclear origin and disturbed consciousness

# What Genes and Disorders Are Targeted?

CentoMetabolic targets close to 200 IMDs. The content and design of the panel is based on our continuously enhanced medical expertise and knowledge of rare metabolic disorders.

The table below shows the distribution of genes and targeted metabolic disorders depending on 18 different disease categories:

| TYPE OF METABOLIC DISORDERS COVERED | # GENES |
|---|---|
| Congenital disorders of glycosylation and other disorders of protein modification | 2 |
| Defects in cholesterol and lipoprotein metabolism | 2 |
| Defects in hormone biogenesis or function | 7 |
| Disorder of phosphate, calcium, and vitamin D metabolism | 3 |
| Disorders in the metabolism of purines, pyrimidines, and nucleotides | 6 |
| Disorders in the metabolism of trace elements and metals | 6 |
| Disorders in the metabolism of vitamins and (non-protein) cofactors | 10 |
| Disorders of amino acid and peptide metabolism | 33 |

| TYPE OF METABOLIC DISORDERS COVERED | # GENES |
|---|---|
| Disorders of carbohydrate metabolism | 35 |
| Disorders of energy metabolism | 6 |
| Disorders of fatty acid and ketone body metabolism | 3 |
| Disorders of lipid and lipoprotein metabolism | 8 |
| Disorders of neurotransmitter metabolism | 1 |
| Disorders of porphyrin and heme metabolism | 8 |
| Disorders of the metabolism of sterols | 16 |
| Lysosomal disorders | 48 |
| Peroxisomal disorders | 16 |
| Porphyria and bilirubinemia | 1 |

## Genes Included (206)

ABCA1, ABCB4, ABCC2, ABCD1, ABCD4, ABCG5, ABCG8, ACAT1, ADA, AGA, AGL, AGPS, AGXT, ALAD, ALAS2, ALDH4A1, ALDOA, ALDOB, ALG3, ALPL, ANTXR2, APOA2, APOA5, APOB, APOC2, APOE, ARG1, ARSA, ARSB, ASAH1, ASL, ASS1, ATP7A, ATP7B, BCKDHA, BCKDHB, BTD, CBS, CD320, CETP, CLN3, CLN5, CLN6, CLN8, CPOX, CPS1, CPT1A, CTNS, CTSA, CTSD, CTSK, CYP11B1, CYP17A1, CYP19A1, CYP21A2, DBT, DDC, DHCR7, DIABLO, DLX4, DNAJC5, DPYD, ENO3, ENPP1, EPHX2, ETHE1, FAH, FBP1, FECH, FGF23, FUCA1, G6PC, G6PD, GAA, GALC, GALE, GALK1, GALNS, GALT, GAMT, GATM, GBA, GBE1, GHR, GK, GLA, GLB1, GM2A, GNPAT, GNPTAB, GNPTG, GNS, GUSB, GYG1, GYS1, GYS2, HCFC1, HEXA, HEXB, HFE, HJV, HGD, HGSNAT, HLCS, HMBS, HPD, HPRT1, HSD3B2, HYAL1, IDS, IDUA, ITIH4, IVD, KHK, LAMP2, LCAT, LDHA, LDLR, LDLRAP1, LIPA, LIPC, LIPI, LMBRD1, LPA, LPL, MAN2B1, MANBA, MCOLN1, MFSD8, MMAA, MMAB, MMACHC, MMADHC, MMUT, NAGA, NAGLU, NAGS, NEU1, NPC1, NPC2, OTC, PAH, PCSK9, PDHB, PEX1, PEX10, PEX12, PEX13, PEX14, PEX16, PEX19, PEX2, PEX26, PEX3, PEX5, PEX6, PEX7, PFKM, PGAM2, PGK1, PGM1, PHKA1, PHKA2, PHKB, PHKG2, PKLR, PNPO, POR, PPOX, PPP1R17, PPT1, PRKAG2, PSAP, PYGL, PYGM, RBCK1, SGSH, SI, SLC17A5, SLC22A5, SLC25A13, SLC25A15, SLC25A20, SLC25A36, SLC2A1, SLC2A2, SLC2A3, SLC37A4, SLC3A1, SLC3A2, SLC40A1, SLC6A19, SLC6A8, SLC7A7, SLC7A9, SLCO1B1, SLCO1B3, SMPD1, SUMF1, TAT, TFR2, TPP1, UGT1A1, UMPS, UROD, UROS

# CENTOGENE´s Biomarker and Enzyme Testing – Going Beyond Genetics

Biomarkers serve as measurable indicators of pathological processes. They are typically directly linked to genetic variants in specific genes and can predict, diagnose, monitor, and assess the severity of a disease. Measuring the cellular activity of an enzyme can also be used as a tool for the diagnosis and monitoring of a disease, as well as treatment efficacy.

Our multiomic- and big data-based approaches allow us to continuously discover new highly specific biomarkers. Any new biomarker will be included in this panel and represents an opportunity to advance our understanding of metabolic diseases as well as develop better tailored therapies for patients.

## Diseases and Complementary Enzymes

### SPHINGOLIPIDOSES AND OLIGOSACCHARIDOSES

- Wolman disease
  Acid lipase
- Pompe disease
  Acidic alpha-glucosidase
- Niemann-Pick disease types A/B
  Acidic sphingomyelinase
- Alpha-fucosidase deficiency
  Alpha-fucosidase
- Fabry disease
  Alpha-galactosidase
- Alpha-mannosidase deficiency
  Alpha-mannosidase
- Schindler/Kanzaki disease
  Alpha-N-acetylgalactosaminidase
- Metachromatic leukodystrophy (MLD)
  Arylsulfatase A*
- Gaucher disease
  Beta-glucocerebrosidase
- Tay-Sachs disease
  Beta-hexasaminidase
- Beta-mannosidase deficiency
  Beta-mannosidase
- Krabbe disease
  Galactocerebrosidase
- Sandhoff disease
  Total hexaminidisase

### NCLs

- NCL1
  Palmitoyl-protein- thioesterase
- NCL2
  Tripeptidyl peptidase

### MPS

- MPS I
  Alpha-L-iduronidase
- MPS II
  Iduronate-2-sulfatase
- MPS IIIB
  N-acetyl-alpha-glucosaminidase
- MPS IVA
  N-acetylgalactosamine-6-sulfate-sulfatase
- MPS IVB
  Beta-galactosidase
- MPS VI
  Arylsulfatase B
- MPS VII
  Beta-glucuronidase

## Diseases and Complementary Biomarkers

- Farber disease
  C26-ceramide
- Gaucher disease
  Glucosylsphingosine (lyso-Gb1)[1]
- Fabry disease
  Globotriaosylceramide (lyso-Gb3)
- Niemann-Pick disease type A/B/C
  Lyso-SM509
- AADC deficiency
  3-O-Methyldopa (3-OMD)

**AADC** Aromatic L-amino acid decarboxylase

**MPS** Mucopolysaccharidosis

**NCLs** Neuronal Ceroid Lipofuscinosis

1 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.

* Patients who qualify for Arylsulfatase A enzyme (MLD) testing will be contacted for submission of additional sample. Arylsulfatase A enzyme (MLD) testing requires ≥ 5 ml EDTA blood (testing is performed in leukocytes). Samples have to arrive within 72 h of collection.

# Key Features and Performance

| | |
|---|---|
| **# GENES** | 206 |
| **CONDITIONS** | > 180 metabolic disorders |
| **COVERAGE** | • All coding regions +/- 10 bp exon / intron boundaries<br>• All relevant deep intronic mutations described in our rare disease-centric Bio/Databank and HGMD® incl. ≥ 99.5 % of targeted regions covered at ≥ 20 x<br>• Specificity > 99.9 % for all reported variants |
| **COMPLEMENTARY TESTING** | Biomarker and enzyme analysis (if applicable)<br>CNV analysis included |
| **MATERIAL** | ≥ 1 filtercard |
| **TAT** | 15 business days |