CENTOGENE
THE RARE DISEASE COMPANY

Biomarkers

PAVING THE WAY TO PERSONALIZED THERAPIES

CENTOGENE's Approach to **Improve Diagnosis of Rare Diseases** and **Accelerate Drug Development**

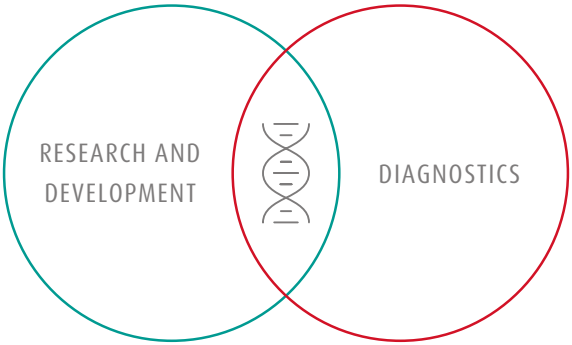
At CENTOGENE, we have a lifetime commitment to the patients we serve. We strive to have an efficient and precise path to diagnosing rare diseases, and we partner with drug-developers to support the efforts to **bring new therapies to patients faster**.

Patients and their families are central to our efforts to **continuously improve rare disease diagnosis and accelerate therapy discovery and development**. Patients globally have provided consent for their samples and **data to be used in an pseudonymized form** for research and development. We are grateful for their participation.

Based on the vast amount of data, a state-of-the-art mass spectrometry-based discovery platform, and complemented by powerful artificial intelligence tools, we continuously search for and discover new disease specific targets, biomarkers, as well as metabolomic and proteomic profiles. Our global network of physicians and clinical collaborators helps us to rapidly validate and refine our **new biomarkers and diagnostic approaches in well-designed clinical studies**, in all phases of development (see https://clinicaltrials.gov for details).

CREATING SOLUTIONS

that help pharmaceutical companies to accelerate the development of orphan drugs: disease understanding, patient identification and screening, as well as biomarker and companion diagnostics programs



RAPID MEDICAL DIAGNOSIS

of rare hereditary diseases through the broadest genetic testing portfolio combined with enzymatic and biomarker testing, and best-in-class interpretation

Role of Enzymatic Essays and Biomarkers in Diagnostics and Therapeutics

Genetics can help to unlock the molecular understanding of disease causes. However, critical insights come with understanding the consequences of genetic variants for protein expression, protein functioning, and cellular dynamics. Measuring the levels of primary proteins and enzyme activity, as well as the concentrations of their metabolites, is of tremendous value in **supporting the classification** of unknown and pathogenic genetic variants. Additionally, **biomarkers play a vital role in the diagnosis of diseases as well as monitoring severity, progression, and treatment efficacy.**

CENTOGENE's **Multiomics platform** adds value from the bench to the clinic

	DRUG DISCOVERY	PRE-CLINICAL / CILINICAL DEVELOPMENT	COMMERCIALIZATION AND CLINICAL DIAGNOSTICS
SOLUTIONS	• Target Discovery & Validation • Elucidating pathological pathways • Screening drug candidates • Selection of lead drug candidate	• Patient identification and recruitment for clinical studies • Patient stratification • Monitoring response to therapy • Potential end-points for regulatory approval	• Early and accurate diagnosis • Screening of high-risk populations • Quantification of disease burden • Monitoring response to treatment • Guiding individualized treatment regimen for improved outcomes
BENEFITS	✓ Novel targets and specific drug candidates ✓ Accelerated clinical trial recruitment ✓ Reducing development risk ✓ Lowered cost ✓ Optimized trial design and treatment regimen ✓ Faster time to market		✓ Earlier diagnosis ✓ Improved treatment outcomes ✓ Increased market traction

Testing Strategies - Fast and Accurate

In complex diseases and disease pathways, a genetic test alone typically can´t provide the information needed for a final diagnosis. Therefore, **CENTOGENE has pioneered the combination of different tests**, like biomarker and multi biomarker patterns with clear recommendations for testing strategies.[1] These testing strategies offer you and your patients a faster, more reliable, and more complete solution – providing vital and time-sensitive answers when they matter the most.

	GENETIC PANEL + BIOMARKER / ENZYME	ENZYME / BIOMARKER + SINGLE GENE ANALYSIS	BIOMARKER	ENZYME PANELS
STRATEGY	Testing a comprehensive range of genes (panel) first, followed by biochemical testing[2]	Biochemical testing combined with single gene testing	Biomarker testing (pre or post diagnosis)	Enzyme testing with optional reflex to genetics
CENTOGENE PRODUCTS	CentoMetabolic® (~200 metabolic disorders) For more info please visit www.centogene.com/diagnostics/metabolic-testing Other panels (then reflex to relevant biomarkers upon request)	For overview please refer to page 8-9 Customised solutions in pharmaceutical collaborations	Biomarkers for eight diseases including AADC deficiency, hereditary angioedema (HAE), Fabry disease, Farber disease, Gaucher disease, Gaucher disease atypical, Niemann-Pick disease (NPD) A/B, and NPD type C More than 50 biomarkers in development	Four enzyme panels: CentoMPS®[3] CentoSphingo®[3] CentoNCL®[3] CentoLSD[3] Optional reflex to genetics (X-TRA[4])

[1] By combining genetic and biochemical testing CENTOGENE follows the recommendation of the American College of Medical Genetics and Genomics (ACMG).
[2] Biomarker/Enzyme testing complementary to support the classification of unknown and pathogenic variants.
[3] For details please go to www.centoportal.com and type‚enzyme panel' in the search field.
[4] The enzyme panels listed above can be requested together with an automatic reflex to genetic testing if an enzyme deficiency is identified via CENTOGENE's "Enzyme Panel X-TRA" option.

When to use it?

GENETIC PANEL + BIOMARKER / ENZYME

- Suspected metabolic disorder
- Complex, overlapping symptoms with broad differential diagnosis
- Abnormal new-born screening results
- Admission to a neonatal intensive care unit
- Symptoms related to neurological conditions of unknown etymology
- Overlapping symptoms with varying age of onset and severity

ENZYME / BIOMARKER + SINGLE GENE ANALYSIS

- Suspected specific disorder
- Clearly definable symptoms
- Follow-up monitoring

BIOMARKER

- Differential diagnosis
- At-risk cohort testing, patient identification
- Disease progression monitoring
- Measure response to treatment
- Guide therapeutic regimen
- Follow-up monitoring

ENZYME PANELS

- At-risk cohort testing

CENTOGENE's Unique Expertise in Metabolic Disorders

Metabolic diseases are a group of rare, inherited diseases characterized by abnormal accumulation of different metabolites in the cells, leading to impaired functioning of the affected cellular organells. A further subgroup, Lysosomal storage disorders (LSDs), collectively affect 1 in 5,000 live births, with Fabry and Gaucher disease being the most prevalent.[5,6,7] It is estimated that **every 20 minutes a child is born with an inherited LSD**.

With effective therapy becoming available for some LSD, early diagnosis is critically important. CENTOGENE has developed multiple specific biomarkers for certain LSDs with therapeutic options. **All analyses can be done from dried blood spots with CentoCard® and help with the early diagnosis, as well as disease progression and therapeutic monitoring of a specific disorder** in the most effective manner.

BIOMARKER DETERMINATION	DISEASE	GENES	DETECTION METHOD
Glucosylsphingosine (Lyso-Gb1)	Gaucher disease	GBA, PSAP	Tandem-MS
Lyso-Ceramide trihexoside (Lyso-Gb3)	Fabry disease	GLA	Tandem-MS
Lyso-SM-509 Lyso-SM-465	Niemann-Pick disease (A/B/C1/C2)	SMPD1, NPC1, NPC2	Tandem-MS
C26-Ceramide	Farber disease	ASAH1	Tandem-MS

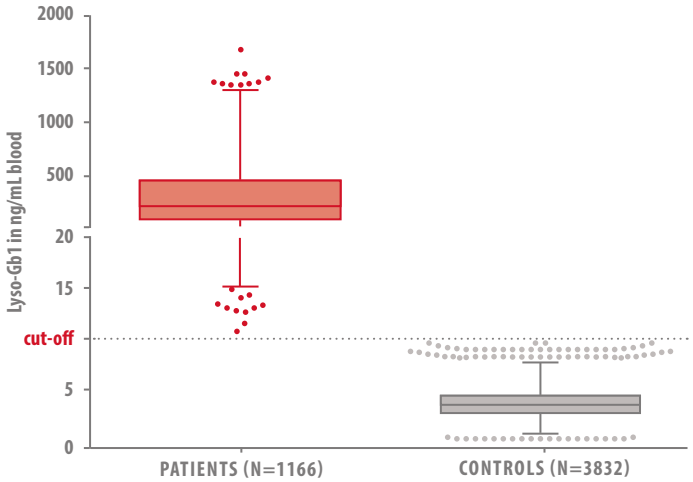
For Gaucher patients in particular, CENTOGENE offers an easy to use smartphone app to help monitoring and managing treatment: **myLSDapp**. Please go to **www.centogene.com/mylsdapp-service** to find out more.

[5] Wittmann, Judit, et al. „Newborn screening for lysosomal storage disorders in Hungary." JIMD Reports-Case and Research Reports, 2012/3. Springer, Berlin, Heidelberg, 2012. 117-125.
[6] Burlina, Alberto B., et al. „Newborn screening for lysosomal storage disorders by tandem mass spectrometry in North East Italy." Journal of Inherited Metabolic Disease: Official Journal of the Society for the Study of Inborn Errors of Metabolism 41.2 (2018): 209-219.
[7] Platt, Frances M., et al. „Lysosomal storage diseases." Nature Reviews Disease Primers 4.1 (2018): 1-25.

Success Story: Biomarker Lyso-Gb1 for Gaucher Disease

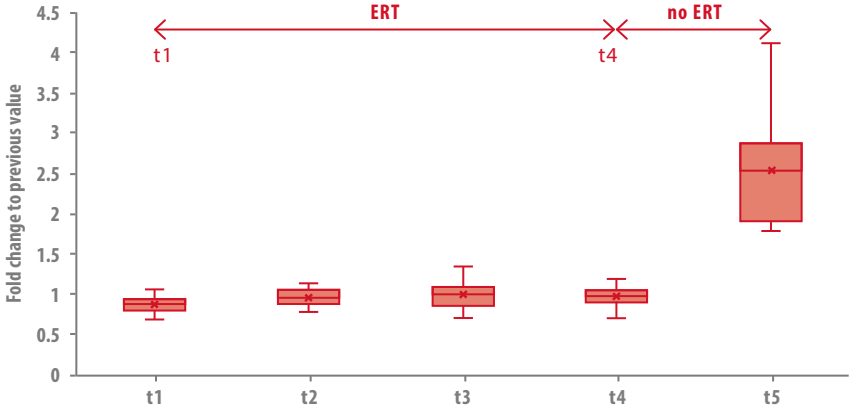
Lyso-Gb1 has been identified as the most precise biomarker for Gaucher disease (GD).[8] With a sensitivity and specificity of 100% (see below), it is the optimal biomarker for a sensitive and reliable diagnosis of GD. Evidence of patient data also proves that quantitation of this biomarker can serve as a direct indicator of disease burden and response to treatment for monitoring GD.[8]

LYSO-GB1 QUANTIFICATION IN GAUCHER PATIENTS AND CONTROLS



100% sensitivity and 100% specificity of Lyso-Gb1 leading to highest accuracy in patient identification for an optimal diagnosis.

LYSO-GB1 LEVELS IN GAUCHER PATIENTS ON THERAPY (N=19, MEAN ΔT BETWEEN T1-T5 = 6 WEEKS)



Lyso-Gb1 levels significantly and rapidly increase at time point t5 after a forced treatment break due to temporary unavailability of enzyme replacement therapy. Lyso-Gb1 thereby proves its superb capabilities for monitoring Gaucher disease.

[8] Elstein, Deborah, et al. „Reductions in glucosylsphingosine (lyso-Gb1) in treatment-naïve and previously treated patients receiving velaglucerase alfa for type 1 Gaucher disease: Data from phase 3 clinical trials." Molecular genetics and metabolism 122.1-2 (2017): 113-120.

CENTOGENE's Biomarker - A Growing Portfolio

	DISORDER COVERED BY CENTOGENE	ENZYMATIC TESTING (ENZYME PANEL)	BIOMARKER TESTING[9]	SINGLE GENE ANALYSIS
SPHINGOLIPIDOSES	Fabry disease	Alpha-galactosidase (CentoLSD, CentoSphingo®)	Globotriaosylsphingosine (Lyso-Gb3) + others in development[9]	GLA
	Farber disease	—	C26-Ceramide	ASAH1
	Gaucher disease type I, II, III	Beta-glucocerebrosidase (CentoLSD, CentoSphingo®)	Glucosylsphingosine (Lyso-Gb1)[10]	GBA
	Gaucher disease, atypical	—	Glucosylsphingosine (Lyso-Gb1)[10]	PSAP
	Krabbe disease	Galactocerebrosidase	In development[9]	GALC
	Metachromatic Leukodystrophy	Arylsulfatase A	In development[9]	ARSA
	Niemann-Pick disease A/B	Acidic sphingomyelinase (CentoLSD, CentoSphingo®)	Lyso-SM-509 & Lyso-SM-465	SMPD1
	Niemann-Pick disease C1/C2	—	Lyso-SM-509 & Lyso-SM-465	NPC1/NPC2
OTHERS (EXCERPT)	Aromatic L-amino acid decarboxylase (AADC) deficiency	—	3-O-Methyldopa (3-OMD)	DDC
	Hereditary angioedema (SERPING1 mutation)	—	C4 and C1-INH complement protein, cleaved high-molecular-weight kininogen (cHMWK) + others in development[9]	SERPING1
	Transthyretin Amyloidosis (TTR)	—	In development[9]	TTR
	Duchenne	—	In development[9]	DMD

(Status: March. 2020)

[9] Further biomarker developments upon request. Over 50 additional biomarkers in development.

[10] Lyso-Gb1 has been identified as the most effective biomarker for Gaucher disease (Elstein, Deborah, et al. "Reductions in glucosylsphingosine (lyso-Gb1) in treatment-naïve and previously treated patients receiving velaglucerase alfa for type 1 Gaucher disease: Data from phase 3 clinical trials." Molecular genetics and metabolism 122.1-2 (2017): 113-120.)

CentoMetabolic®

CENTOGENE is committed to developing innovative solutions to help end the diagnostic odyssey of patients suffering from rare genetic diseases. Our multiomic panel, CentoMetabolic®, has been designed to test for a wide range of metabolic disorders. It **integrates genetic and biochemical testing,** including enzyme assays as well as a selection of proprietary biomarkers. If genetic variants relevant to your patient are detected in the broad genes covered by CentoMetabolic®, we will **automatically include biomarker and/or enzyme testing** (if applicable) and include the results in your medical report. These results can help to determine disease status and severity as well as treatment options.

CentoMetabolic® combines genetic and biochemical testing to provide the most comprehensive screening for rare metabolic conditions.

Why Choose CentoMetabolic®?

- Fast and precise diagnosis with TAT of < 15 days
- Comprehensive coverage of almost 200 diseases
- Complementary biochemical testing with selected biomarkers and enzyme-activity assays
- World-class medical reports interpreted by expert human geneticists
- Cost-effective

Please go to **www.centogene.com/diagnostics/metabolic-testing** to find out more.

CENTOGENE is focused on transforming clinical, genetic and biochemical data into medical solutions for patients.

We are committed to helping patients affected by rare diseases through unlocking the knowledge gained from our vast experience in the diagnoses of more than 3,700 genetic diseases. Based on this insight, we are developing innovative biomarkers and completely new testing strategies. Our mission is to accelerate the development of new therapies for rare genetic diseases and thereby to improve the outcomes for patients and their families.

CENTOGENE, **the rare disease company.**

THE CENTOGENE Advantage – A Comprehensive R&D Solution Beyond Lab Testing

Our solutions go beyond laboratory testing and medical interpretation – leveraging our biobank, our global clinical network, and deep medical expertise based on curated medical knowledge. We have proven capabilities in the identification and development of new biomarkers, with more than ten commercialized biomarkers[11] and a strong pipeline of over 50 in development.

- Providing a broad range of research, patient recruitment, and testing solutions to **over 35 pharmaceutical partners**[12]
- A global network of **more than 37,000 physicians/experts** in rare disease from **over 120 countries** with access to relevant patient populations
- **State-of-the-art IT-infrastructures**, adhering to strictest international guidelines and legislations on data privacy, compliant to the European General Data Protection Rules (**GDPR**) and US **HIPAA.**[13, 14]

Data interpretation with **CentoMD®**, which we believe is the world's largest curated mutation database for rare diseases with over 12 million unique variants and more than **400,000 analysed cases** in **over 120 countries**.

We simplify logistics with **CentoCard®:** our **CE-marked dried blood spot collection** device makes it almost **as easy as sending a postcard**. Samples collected on CentoCard® are not sensitive to shipping time or temperature and can be mailed via regular post. CentoCard® provides a single sample for complete patient diagnostics: enzyme assay, biomarker analysis and genetic testing.

CentoPortal® is a single point **24/7 web service** – serving as a secure online resource with the highest data protection and privacy standards. With CentoPortal®, you can order and distribute CENTOGENE's unique filter cards – CentoCard®, document patient consent, obtain an overview of your patients and open orders, as well as access and share reports.

[11] Please see overview on page 8.
[12] Please see www.centogene.com/pharma for details.
[13] Please see www.centogene.com/diagnostics/privacy-policy for details.
[14] US HIPAA compliant for US samples.

Your partner of choice

For further information and support, please contact our closest representative or our customer support team, easily accessible by phone or email.

www.centogene.com

CONTACT DETAILS:

CENTOGENE GmbH
Am Strande 7
18055 Rostock
Germany

CENTOGENE GmbH is a subsidiary of CENTOGENE N.V.

PARTNER SUPPORT

customer.support@centogene.com
+49 (0) 381 80 113 - 416
+49 (0) 381 80 113 - 401

FOR U.S PARTNERS

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

Rostock - CLIA #99D2049715

Cambridge - CLIA #22D2154474

V4eng_July2020