CENTOGENE
THE RARE DISEASE COMPANY

Genetic Diagnostics

› A. Analysis Requested (please choose type here and specify your order below)

- ☐ CentoICU Platinum OR Platinum Plus
- ☐ CentoMito Genome
- ☐ Cento Array Cyto HD
- ☐ Cento Array Cyto 750K
- ☐ NGS Panel
- ☐ NGS Panel Plus
- ☐ NGS Panel Genomic
- ☐ Single Gene Sequencing

Additional Testing

- ☐ Deletion/Duplication Analysis
- ☐ Repeat Expansion
- ☐ Carrier Testing
- ☐ Hot Spot testing

Details for requested test (mandatory) .....

Requested reflexive test (optional, if any) .....

› B. Patient Name (Label)

Last Name .....

First Name .....

Date of Birth MM DD YYYY

Sex ☐ Male ☐ Female

Street/No/App. .....

Town/State/ZIP .....

Country USA

Medical Reference Number .....

Sample Date MM DD YYYY (Not required if phlebotomy service ordered)

Home Phone ..... Cell .....

E-Mail .....

› C. Ordering Physician (Reporting Address)

Name of Physician .....

Organization/Institution .....

Point of Contact .....

Street .....

Town/State/ZIP .....

Country USA

Phone ..... Fax .....

E-Mail .....

› D. Additional clinical or laboratory contact (optional)

Name .....

Organization/Institution .....

E-Mail .....

› E. Billing

☐ **Direct patient billing**

The Patient was informed about the resulting costs and agrees on direct billing. CENTOGENE will send an electronic invoice to the Patient email listed above.

☐ **Commercial insurance or third-party billing***

* Please include a copy of the front and back of insurance card

Name /Insurance Company .....

Subscriber name .....

Member ID# .....

Relationship to subscriber .....

☐ **Institutional billing**

Billing contact name .....

Phone ..... Fax .....

E-Mail .....

Billing address .....

City .....

State ..... Zip Code .....

Patient has been informed and authorizes CENTOGENE to release information concerning testing to his her health insurance and/or an insurance payment consultant in order to process and/or support claims of the Patient for insurance payment. I confirm that I offered pre-test genetic counselling to the Patient if required by his/her insurance.

Date .....

Signature of Physician ✘ .....

CENTOGENE US, LLC
1500 District Avenue
Burlington, MA 01803, USA

› Contact Details
Customer Service
Phone: (+1) 781-270-1519
Fax: (+1) 781-998-1060
dmqc-us@centogene.com
www.centogene.com

› Actual Materials Needed

Blood & DNA requirements:
≥ 2 µg DNA at a concentration of ≥ 50 ng/µl; or
≥ 1ml EDTA Blood; or
≥1 CentoCard (full 10 spots)

CAP#8005167 CLIA#99D2049715

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MANDATORY

Please provide detailed clinical information

Patient name .....

☐ Age of manifestation .....

☐ Unaffected

Family history:

A. Consanguinity ☐ YES ☐ NO

B. Affected siblings ☐ YES ☐ NO

Pedigree

Clinical information

Please tick the appropriate phenotype(s) ☑

A. NEUROLOGY

1. Behavioral abnormality
- 1.1 Autism
- 1.2 Attention deficit disorder
- 1.3 Psychiatric diseases

2. Brain imaging
- 2.1 Abnormal cortical gyration
- 2.2 Abnormal myelination
- 2.3 Agenesis of corpus callosum
- 2.4 Brain atrophy
- 2.5 Cerebellar hypoplasia
- 2.6 Heterotopia
- 2.7 Holoprosencephaly
- 2.8 Hydrocephalus
- 2.9 Leukodystrophy
- 2.10 Lissencephaly

3. Developmental delay
- 3.1 Delayed language dev.
- 3.2 Delayed motor dev.
- 3.3 Developmental regression
- 3.4 Intellectual disability

4. Movement abnormality
- 4.1 Ataxia
- 4.2 Chorea
- 4.3 Dystonia
- 4.4 Parkinsonism

5. Neuromuscular abnormality
- 5.1 Hyperreflexia
- 5.2 Muscle hypertonia
- 5.3 Muscle hypotonia
- 5.4 Spasticity

6. Seizures
- 6.1 Febrile seizures
- 6.2 Focal seizures
- 6.3 Generalized seizures

7. Others
- 7.1 Craniosynostosis
- 7.2 Dementia
- 7.3 Encephalopathy
- 7.4 Headache
- 7.5 Macrocephaly
- 7.6 Microcephaly
- 7.7 Migraine
- 7.8 Stroke

B. METABOLISM
1. Abnormal creatine kinase
2. Decreased plasma carnitine
3. Hyperalaninemia
4. Hypoglycemia
5. Increased CSF lactate
6. Increased serum pyruvate
7. Ketosis
8. Lactic acidosis
9. Organic aciduria

C. EYE
1. Blepharospasm
2. Cataract
3. Coloboma
4. Glaucoma
5. Microphthalmos
6. Nystagmus
7. Ophthalmoplegia
8. Optic atrophy
9. Ptosis
10. Retinitis pigmentosa
11. Retinoblastoma
12. Strabismus
13. Visual impairment

D. MOUTH, THROAT AND EAR
1. Abnormality of dental color
2. Cleft lip / palate
3. Conductive hearing impair.
4. External ear malformation
5. Hypodontia
6. Sensoneural hearing impair.

E. SKIN, INTEGUMENT AND SKELETAL

1. Skeletal
- 1.1 Abnormal limb morphology
- 1.2 Abnormal vertebral column
- 1.3 Abnormality of the skeletal system
- 1.4 Joint hypermobility
- 1.5 Multiple joint contractures
- 1.6 Polydactyly
- 1.7 Scoliosis
- 1.8 Syndactyly
- 1.9 Talipes equinovarus

2. Skin and integument
- 2.1 Abnormal hair
- 2.2 Abnormal nail
- 2.3 Abnormal skin pigmentation
- 2.4 Hyperextensible skin
- 2.5 Ichthyosis

F. CARDIOVASCULAR
1. Angioedema
2. Aortic dilatation
3. Arrhythmia
4. Atrial septal defect
5. Coarctation of aorta
6. Dilated cardiomyopathy
7. Hypertension
8. Hypertrophic cardiomyopathy
9. Hypotension
10. Lymphedema
11. Malf. of heart and great vessels
12. Myocardial infarction
13. Stroke
14. Tetralogy of Fallot
15. Vasculitis
16. Ventricular septal defect

G. GASTROINTESTINAL, GENITOURINARY, ENDOCRINE

1. Gastrointestinal
- 1.1 Aganglionic megacolon
- 1.2 Constipation
- 1.3 Diarrhea
- 1.4 Gastroschisis
- 1.5 Hepatic failure
- 1.6 Hepatomegaly
- 1.7 High hepatic transaminases
- 1.8 Obesity
- 1.9 Pyloric stenosis
- 1.10 Vomiting

2. Genitourinary
- 2.1 Abnormal renal morphology
- 2.2 Abnormal urinary system
- 2.3 Hydronephrosis
- 2.4 Renal agenesis
- 2.5 Renal cyst
- 2.6 Renal tubular dysfunction

3. Endocrine
- 3.1 Diabetes mellitus
- 3.2 Hyperparathyroidism
- 3.3 Hyperthyroidism
- 3.4 Hypoparathyroidism
- 3.5 Hypothyroidism

H. REPRODUCTION
1. Abnormal external genitalia
2. Abnormal internal genitalia
3. Hypogonadism
4. Hypospadias
5. Infertility

I. ONCOLOGY
1. Adenomatous colonic polyposis
2. Breast carcinoma
3. Colorectal carcinoma
4. Leukemia
5. Myelofibrosis
6. Neoplasm of the lung
7. Neoplasm of the skin
8. Paraganglioma
9. Pheochromocytoma

J. HEMATOLOGY AND IMMUNOLOGY
1. Abnormal hemoglobin
2. Abnormality of coagulation
3. Anemia
4. Immunodeficiency
5. Neutropenia
6. Pancytopenia
7. Splenomegaly
8. Thrombocytopenia

K. PRENATAL AND DEVELOPMENT
1. Abnormal facial shape
2. Failure to thrive
3. Hemihypertrophy
4. Hydrops fetalis
5. IUGR
6. Oligohydramnios
7. Overgrowth
8. Polyhydramnios
9. Premature birth
10. Short stature
11. Tall stature

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Consent form for conducting genetic analyses

It is **mandatory** to ensure that a patient has signed his or her consent to conduct genetic analyses.

This can be given either by:

Part (I): **Signed consent on the part of the patient OR**

Part (II): **Signed confirmation on the part of the physician stating that the signed patient consent exists in the files.**

CENTOGENE needs either Part (I) OR (II) in order to be legally able to conduct genetic analysis.

Please ensure that the applicable document accompanies the sample(s).

Dear patient,

Your physician has recommended for you (or a person for whom you have custody and you care for) a genetic analysis to clarify the following diagnosis/symptoms:

.....

.....

(to be completed by physician)

We would like to explain the purpose of these analyses, what occurs with a genetic test and the importance the results could have for you and your family. For more specific information on the genetic test, please refer to the requisition form.

The purpose of a genetic test is to study your genetic material (DNA) using a molecular-genetic method that has the capability to detect the disease that has occurred or is suspected in you or your family based on changes (called mutations).

In a genetic analysis – depending on the case –

- either individual genetic characteristics for a specific condition or
- many genetic characteristics are investigated at the same time using an overview method (e.g. using exome or genome sequencing).

The study material that is used for your genetic test is stated in the requisition form and is typically blood.

Significance of the results:
If a characteristic result in a disease is demonstrated, this result is usually highly conclusive. If no disease-causing mutation is found, genetic changes responsible for the disease may still exist. A genetic disease or tendency to have a disease can therefore usually not be excluded in full.

Sometimes gene variants are proven but their significance is not clear. This is stated in the results and discussed with you. A comprehensive explanation of all possible causes of diseases due to genetic reasons is not possible.

It is also **not possible to exclude every disease risk** for yourself and your family members (especially your children) utilizing genetic analyses.

The knowledge of the results may result in mental stress. It is always recommended to discuss the details of the genetic report with your local doctor.

Incidental findings:
In principle, results can occur for all testing techniques that are not directly related to the actual issue but may still be of medical importance for you and your family (so-called **incidental findings**). In particular for the overview methods such as genome sequencing, incidental results can occur that relate to higher risks (that you may not be aware of) for potentially serious, unavoidable or non-treatable diseases. As part of the consent you can decide whether and under what circumstances you wish to be informed about such incidental findings.

Family findings:
If several family members are tested, a correct interpretation of the results depends on the assumed relationships being correct. If doubt is created by the genetic analysis about the apparent relationships, we will in general not inform you, to protect the privacy of the involved individuals. An exception will be made if it is absolutely necessary for the completion of the requested test.

Use of the sample/results:
The sample and the test results will be used for the analysis and in accordance with your consent declaration that is stated below. The test results will also be used - if possible - for treatment decisions by your physician(s).

Right of revocation:
You can withdraw your consent to the analysis/examination with effect for the future at any time in full or in part without stating reasons.

Right not to know:
You have the right not to be informed about test results (right not to know), to stop the testing processes that have been started at any time up to being given the results and to request the destruction of all test/examination results not already known to you.

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PATIENT COPY

Part (I): Declaration of consent
(please read this carefully)

MANDATORY

Name of patient: .....

Disease/genetic test: .....
(to be filled in by the physician)

By signing this declaration of consent I acknowledge that I have:

- received, read and understood the preceding written explanation of genetic analyses and the further explanation contained in the requisition form; and
- received appropriate explanations (from my physician) with regard to the disease and the genetic basis, purpose, scope, type, significance and achievable results by and limitations of the planned test, importance of the analyzed genetic characteristics for my disease/health disturbance, possibilities of prevention/ treatment of a disease or a health disturbance, planned use of the sample (including processed samples) and of the test results as well as with regard to risks associated with (1) the generation of the sample required for the genetic testing and (2) the knowledge of the results of the genetic testing. All my questions have been answered and I have had the necessary consideration time.

With my signature at the end of this declaration I consent to

(1) the genetic analysis by CENTOGENE AG (Germany) and/or CENTOGENE US, LLC (USA) (together "CENTOGENE Group") for the subject stated above as explained to me in detail by my physician, (2) the collection, processing, use and transfer (also electronically and across country borders) of my personal data (also partially health related) and sample by and between my physician, the CENTOGENE Group and its companies for the purposes stated in this consent form, (3) generation of the necessary sample, (4) storage and use of the sample for up to 10 years to be able to verify/check the results, (5) add to my record and use for the above purposes – if applicable – personal data on members of my family – if these members have consented, (6) inform me or my physician or a laboratory acting on behalf of my physician about the results of the genetic analysis, (7) provide upon my separate request to me, my physician or the instructing laboratory the raw data of the genetic analysis and (8) to share my personal data – but only to the extent absolutely necessary – with further parties, insofar as this relates to (i) acquiring the necessary blood sample for testing, e.g. through a phlebotomy service, (ii) health insurance review and invoicing of the genetic testing by a third party in my country towards me or my insurance, or (iii) reasons of reimbursement by my health insurance. I also release CENTOGENE Group and its employees from their secrecy obligations as physicians or healthcare professionals vis-à-vis service and external data storage providers that administer, maintain and provide systems, databases, software and external data storage to CENTOGENE Group.

I am aware that I can revoke my consent in full or in part at any time with effect for the future without stating reasons and that I have the right not to know as described in the preceding written explanation. I may stop the testing processes at any time up to being given the results and may request the destruction of all test/examination results not already known to me.

Place, Date .....

OPTIONAL

I also optionally grant my consent as follows (please tick "yes" or "no"):

Incidental findings

Whole exome (WES) and whole genome sequencing (WGS) tests are analyzing numerous different genes. It is therefore possible to discover incidental findings that are not necessarily related to the reason for ordering the WES/WGS test. Such findings can provide information not anticipated and unrelated to your reported clinical symptoms, but can be of medical value for patient care.
I agree, that CENTOGENE Group generally reports mutations of the specified classes or types in the genes in accordance with the "ACMG Recommendations for Reporting of Incidental Findings". However, I agree, that CENTOGENE Group may in its sole discretion also report (other) incidental findings in other cases or refrain from reporting incidental findings although this is recommended as per the said recommendations.

☐ **YES** ☐ **NO**

Further storage and use of personal data, results and samples

The retention, storage and further usage of my personal data (e.g. name, birthday, address, description and symptoms of the disease), the personal data of members of my family (e.g. names and the symptoms of the disease) – if these members have consented –, and the results of the genetic analysis and examination (all together the "**Personal Information**"), as well as the original and processed samples (together the "**Remaining Samples**") may be useful for further advising/testing me and/or my family members, verification/checking of results or other requests, quality assurance and the tracking of latest scientific findings as well as for internal and external research in the field of genetic diseases and of biological mechanisms that may lead to diseases, thereby possibly improving the diagnosis and treatment of genetic diseases (e.g. by developing biomarkers) (together the "**Purposes**").

I therefore agree, that CENTOGENE Group

- stores Personal Information and Remaining Samples for a period of at least 20 years and uses these for the Purposes and related research or commercial matters whereby Personal Information will not be shared with any third party outside the CENTOGENE Group without my prior explicit consent;

☐ **YES** ☐ **NO**

- uses the Personal Information in anonymous or pseudonymous form (pseudonymous internally at CENTOGENE Group) in a database in which a huge number of results of genetic tests are stored and provides (commercial) access to this database to external physicians, scientists, researchers and (pharmaceutical) companies. The test results contained in the database are anonymous for the physicians, scientists, researchers and companies. Anonymized test results in CENTOGENE Group's databases cannot be destroyed as they become unidentifiable and untraceable after their input into CENTOGENE Group's databases.

☐ **YES** ☐ **NO**

Signature of Patient/Guardian ✗ .....

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PHYSICIAN COPY

Part (II): Confirmation of patient consent by physician

MANDATORY

Name of patient: .....

DOB: MM DD YYYY .....

Patient-ID: .....
(please provide always at least two identifiers, e.g. name of patient and date of birth)

Examination target: .....

CENTOGENE AG (Germany) and CENTOGENE US, LLC, (USA) (together "**CENTOGENE Group**"), are subject to certain legislation, e.g. German law which requires a specified patient consent form to be signed by the patient for conducting genetic analyses. Such consent may be either given on this consent form or patients declare an individual consent according to local requirements in the local language.

We/I hereby confirm that the following requirements are met with respect to the consent that has been declared by the patient or (as the case may be) his/her legal representative:

- The patient has been duly informed about the disease and the genetic basis, purpose, scope, type and significance of the planned genetic test(s), achievable results by and limitations of the planned test, importance of the analyzed genetic characteristics for his/her disease/health disturbance, possibilities of prevention/treatment of a disease or a health disturbance, planned use of the sample (including processed samples) and of the test results as well as with regard to risks associated with (1) the generation of the sample required for the genetic testing and (2) the knowledge of the results of the genetic testing.
- We/I will ensure that the test results will be interpreted to the patient in an appropriate manner and with accompanying counseling.
- The patient was informed that she/he has the right to revoke his/her consent at any time with effect for the future and not to be informed about test results (right not to know), to stop the testing processes that have been started at any time up to being given the results and to request the destruction of all test/examination results not already known to him/her.

We/I confirm the patient is legally capable of providing this consent (respectively that the consent was given by an authorized representative), has/had all questions answered, has/had the necessary consideration time and has not exercised his right not to know.

We/I confirm that the patient has consented to (1) the genetic analysis by CENTOGENE AG (Germany) and/or CENTOGENE US, LLC (USA) (together "CENTOGENE Group") for the subject stated above, (2) the collection, processing, use and transfer (also electronically and across country borders) of his/her personal data (also partially health related) and sample by and between my physician, the CENTOGENE Group and its companies for the purposes stated above, (3) generation of the sample, (4) storage and use of the sample for up to 10 years to be able to verify/check the results, (5) adding to his/her record and using for the above purposes personal data on members of his/her family – if these members have consented – , (6) inform him/her, us/me or a laboratory acting on our/my behalf about the results of the genetic analysis, (7) provide upon his/her separate request to him, us/me or the instructing laboratory the raw data of the genetic analysis and (8) to share his/her personal data with further parties, insofar as this relates to (i) acquiring the necessary blood sample for testing, e.g. through a phlebotomy service, (ii) health insurance review and invoicing of the genetic testing by a third party in the patient's country towards him/her or his/her insurance, or (iii) reasons of reimbursement by patient's health insurance. We/I confirm that the patient has released CENTOGENE Group and its employees from their secrecy obligations as physician or healthcare professional vis-à-vis service and external data storage providers that administer, maintain and provide systems, databases, software and external storage to CENTOGENE Group or provide external data storage to CENTOGENE Group.

OPTIONAL

Furthermore, we/I confirm that the patient optionally consented as follows:

Incidental findings

The patient agrees to be informed about incidental findings of mutations of the specified classes or types in the genes, i.e. findings that are not directly related to the actual issue, in accordance with the "ACMG Recommendations for Reporting of Incidental Findings" and that CENTOGENE Group in its sole discretion may report also (other) incidental findings or refrain from reporting incidental findings although this is recommended as per the said recommendations.

☐ **YES** ☐ **NO**

Further storage and use of personal data, results and samples

The patient was informed about the optional retention, storage and further usage of his/her personal data (e.g. name, birthday, address, description and symptoms of the disease), the personal data of members of his/her family (e.g. names and the symptoms of the disease) – if these members have consented –, and the results of the genetic analysis and examination (all together the "**Personal Information**") as well as the original and processed samples (together the "**Remaining Samples**") for further advising/testing him/her, his/her family members, verification/checking of results or other requests, quality assurance and the tracking of latest scientific findings as well as for internal and external research in the field of genetic diseases and biological mechanisms that may lead to diseases, thus possibly improving diagnosis and treatment of genetic diseases (e.g. by developing biomarkers) (together the "**Purposes**").

The Patient agrees that CENTOGENE Group

- stores Personal Information and Remaining Samples for a period of at least 20 years and uses the Personal Information and Remaining Samples for the Purposes and related research or commercial matters whereby Personal Information will not be shared with any third party outside the CENTOGENE Group without his/her prior explicit consent;

☐ **YES** ☐ **NO**

- uses the Personal Information in anonymous or pseudonymous form (pseudonymous internally at CENTOGENE Group) in a database in which a huge number of results of genetic tests are stored and provides (commercial) access to this database to external physicians, scientists, researchers and (pharmaceutical) companies. The test results contained in the database are anonymous for the physicians, scientists, researchers and companies. Anonymized test results in CENTOGENE Group's databases cannot be destroyed as they become unidentifiable and untraceable after their input into CENTOGENE Group's databases.

☐ **YES** ☐ **NO**

We/I confirm that we/I have the patient's signature on file for all of the issues mentioned above and that we/I are aware that the patient can request us to have his/her results eliminated if they are not already known to him/her at any time and that we/I shall convey this request to CENTOGENE Group. We/I confirm that we/I will retain the consent form signed by the patient for an unlimited period of time and that we will provide CENTOGENE Group with this form upon first request.

Place, Date .....

Name of Physician .....

Signature of Physician ✗ .....

CENTOGENE US, LLC
1500 District Avenue
Burlington, MA 01803, USA

› Contact Details
Customer Service
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