WHOLE EXOME SEQUENCING REQUISITION
PROBAND

1-844-363-4357 · Ask.Genetics@LifeLabs.com

Schillingallee 68 ·18057 Rostock Germany

Attention Patient: Please visit your nearest LifeLabs or CML Healthcare Patient Service Centre for sample collection

CONTRACT #	**LL: K012-01/ CML: CEN**	**LifeLabs Demographic Label**
Report to Physician Billing #		
Ordering Physician Name		
Physician Signature:		
Ordering Physician Address & Contact Info:	Address: Tel: Fax:	
Copy to (name & contact info):	Name: Contact:	
Bill to	**Contract # K012-01** (patient does not pay at time of collection)	**Patient Gender:** (M/F)
Patient Name (Last, First):		**Patient DOB:** (YYYY/MM/DD)
Patient Address:	**Patient Health Card:**	**Patient Telephone:**

Please ship all NON-PRENATAL samples to:
LifeLabs ·Attn CDS Department • 100 International Boulevard• Toronto ON• M9W6J6

TEST REQUESTED

☐ **Genetic Test - Blood Sample** 2 x 4mL EDTA	**LL TR # / CML TC#**
☐ **Genetic Test (Pediatric) - Blood Sample** 1 x 2mL EDTA	**4005**
☐ **Genetic Test - Other Sample Type**	**4008**
PRENATAL SAMPLES: Please ship directly to CENTOGENE.	**4014**

Date Blood Collected (YYYY/MM/DD): _____ **Time Blood Collected** (HH:MM)) :_____ **Collector Name:** _____

CLINICAL FEATURES

Metabolic	Cortical dysplasia	Hypospadias	Growth retardation	Organomaly
Cardiomyopathy	Delayed motor milestones	Infertility	Polydactyly	Paraganglioma
Carnitine reduced	Delayed speech	**Ophthalmological**	Scoliosis	Pheochromocytoma
CK abnormalities	Dystonia	Blepharospasm	Short stature	Pyloric stenosis
CSF lactate increase	Development regression	Cataract	Skeletal abnormalities	Recurrent vomiting
Elevated alanine	Epilepsy, focal	Colobom	Skin tumors	Renal agenesis
Elevated pyruvate	Epilepsy, generalized	Glaucoma	Syndactyly	Renal tubulopathy
Hepatosplenomegaly	Headache	Vision loss	Vertebral anomaly	Splenomegaly
Ketosis	Heterotopia	Ophthalmoplegia	**Cardiological**	**Tumoral and haematological**
Lactic acidemia	Holoprosencephaly	Optic atrophy	Arrhythmia	Adenomatous polyposis
Organic aciduria	Hydrocephalus	Ptosis	Cardiomyopathy	Anemia
Ear, nose and throat	Intellectual disability	Retinitis	Coarctation of aorta	Brain tumor
Deafness	Leukodystrophy	Retinoblastoma	Congenital heart disease	Breast cancer
Ear malformation	Lissencephaly	**Bone, Skin and immune**	Long QT syndrome	Colorectal tumor
Failure to thrive	Mental retardation	Abnormal hair	Septum defect	Immunodeficiency
Vascular	Microcephaly	Abnormal nails	Tetralogy of Fallot	Lung tumor
Angioedema	Migraine	Abnormal pigmentation	**Liver/Kidney/Endocrinology/ Gastrointestinal**	Melanoma
Coagulation disorder	Mitochrondriopathy	Anemia	Constipation	Neurofibromatosis
Hypertension	Muscle weakness	Club foot	Diabetes mellitus	Neutropenia
Hypotension	Parkinson	Dysmorphic features	Diarrhea	Pancytopenia
Infarction	Psychiatric syndromes	Growth retardation	Elevated transaminases	Sickle cell anemia
Stroke	Seizure disorder	Hyperextensibility	Hepatic failure	**Malformation and retardation syndrome**
Vasculitis/angiitis	Spasticity	Ichthyosis	Hepatosplenomegaly	Agenesis of corpus callosum
Neurological	Stroke	Growth retardation	Hirschsprung disease	Brain atrophy
Abnormal movements	**General development failures**	Hyperextensibility	Hypoparathyroidism	Cortical dysplasia
Ataxia	Failure to thrive	Ichthyosis	Hypothyroidism	Dementia
Autism	Intrauterine growth restriction	Immune deficiency	Kidney abnormalities	Hemimegalencephaly
Brain atrophy	Prematurity	Joint contractures	Kidney and endocrine disorders	Hydrocephaly
Chorea	**Reproductive disorders**	Limp malformation	Kidney malformation	Limb malformation
Corpus callosum agenesis	Genital anomalies	Pancytopenia	Obesity/Overgrowth	

**** LIFELABS/CML STAFF: PHOTOCOPY REQUISITION AND INCLUDE 1 COPY WITH SAMPLES****

LifeLabs Genetics

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WHOLE EXOME SEQUENCING REQUISITION
PROBAND

CENTOGENE
THE RARE DISEASE COMPANY
Schillingallee 68 · 18057 Rostock Germany

Patient Name:	**Patient DOB** *(YYYY/MM/DD):*

Patient Information:	Gender: ☐M ☐ F Ethnicity: _____ Relevant Family history: **Have other family members submitted samples to Centogene for analysis?** ☐Y ☐ N If yes, Name:_____ Relationship to patient _____ DOB *(YYYY/MM/DD)*:_____
Sample Type:	☐ ***Blood** (EDTA: 5mL for single gene, 10mL for panel) ☐ **DNA** (single gene:1-10ug, panel 10-100ug) ☐ ***Filter card** (1 card/30 exons: Available by request)
Billing Status:	☐ **Ministry of Health Approved** *(Approval letter attached)* ☐ **Ministry of Health Approval Pending** ☐ **Institution** *(Complete information below)* ☐ **Private Pay** *(Complete information below)*
Institution Billing ONLY:	**Institution Name:** _____ **Contact Name:** _____ **Address:** **Phone:** (____) ____-____ **Fax:** (____) ____-____ **Email:** _____
Private Pay ONLY:	**Credit Card Type:** ☐ **MasterCard** ☐ **Visa** **Card Number**_____ **Exp Date(MM/YY)**_____ **Name (as it appears on credit card)**_____ **I understand that my credit card will be charged for the full amount of testing not paid for by my provincial health plan** **Cardholder Signature:** _____ **Date (DD/MM/YYYY)**_____
Ordering checklist *Each of these are mandatory for Whole Exome Sequencing*	☐ **Proband requisition** ☐ **Clinical Features checklist** ☐ **Informed consent** ☐ **Parental 1 & 2 requisitions**

**** PLEASE INCLUDE A COPY OF REQUISITION WITH SAMPLES ****

Patient Name:	**Patient DOB** *(YYYY/MM/DD):*

Clinical Exome Sequencing – About the Test

☐ **CentoXome®** Bioinformatic analysis and validation of the sequencing results by Sanger sequencing, including an extended clinical report

What is a Whole Exome Sequencing Test?

A new form of genetic testing called Whole Exome Sequencing (WES) identifies changes in DNA by focusing on the most informative regions of the genome. The exome is the collection of those DNA sequences of the genes which determine the production of proteins, which your body needs in order to function properly. Most of the disease causing mutations that science has been able to pinpoint so far are located in exons. Whereas most genetic tests focus on a single gene or a set number of predetermined genes, WES tests examine thousands of genes simultaneously. This is what makes WES one of the most efficient means of testing for the cause of complex genetic problems. WES is ideal to find novel mutations and identify atypical presentations of a disease.

Test Reports

When an exome sequence is analyzed, it is compared to the reference human genome. While there are always certain variations, depending upon the individual and the data available for disease causing mutations which can be found by comparing data with medical databases and looking for scientific links. If your WES test reveals any potentially disruptive variations or problems which may be related to a certain medical condition, this would be reported to your physician. Such medical reports may be supplemented with additional information, including:

Findings that require medical steps

A medical report may include information that is considered to be important because this is of direct and immediate relevance, either to your own health or to that of family members who share part of your genetic background. In deciding which information to include in the report, CENTOGENE adheres to the guidelines set out by the American College of Medical Genetics (ACMG), which allow for reporting specific types of medically actionable or incidental findings (PMID: 23788249). This list of genes at the ACMG is constantly being updated to include all such instances of mutations which are seen as being relevant to patients. If any mutations are found which match those on the ACMG list, these will be reported to your physician.

In addition, CENTOGENE also makes use of its own Mutation Database (CentoMD®), which encompasses over 12,000 mutations collected from a global population. Our medical colleagues may recognize other genes which might be of medical significance, and these can be reported as well. Should you not wish to receive this information in your report, it is possible to opt out of this service.

CENTOGENE adheres to the "ACMG Recommendations for Reporting of Incidental Findings" and will not report on findings not directly related to the cause of a disease and not listed in the ACMG guidelines.

Findings confirmed by Sanger sequencing

CENTOGENE uses Sanger sequencing to confirm WES findings when necessary. Sanger sequencing is still the golden standard for the confirmation of detected mutations.

- When examining deleterious mutations related to patient phenotype.
- In cases where at least one parent's sample is provided, to examine VUS (variants of unclear clinical significance) related to the phenotype with an established autosomal dominant inheritance pattern.
- In cases where at least one parent's sample is provided and there are 2 variant alleles, to examine VUS related to phenotype with established autosomal recessive inheritance.
- In cases where at least one parent's sample is provided and there is an established X-linked inheritance.
- When examining mutations requiring medical action.
- With mutations identified in the mitochondrial genome.
- Other instances in which Sanger is seen as a useful and reliable tool.

Use of biological parental samples in the testing process

Biological parental samples can help improve results in WES testing. Although CENTOGENE does not perform direct testing on these samples, they are examined using other targeted methods. We look for mutations and/or variants which have a high probability of causing disease in order to confirm the mode of inheritance or a de novo status. There is no charge for examination of these samples. The parental status for carrier mutations recommended for reproductive screening is also reported (always confirmed by Sanger sequencing), but a separate parental report is not issued.

Possible risks and things you should know

1) WES testing does not analyze all genes in the human genome. Some genes cannot be examined because of various technical reasons.
2) You may have a mutation in one of the genes included in the test, but it is not always possible to detect all mutations with WES methods. This means that a patient can be affected with a certain condition, but that WES testing does not identify or reveal this.
3) WES testing encompasses many different genes and looks for a variety of conditions and diseases. Such test may reveal genetic information about yourself or a family member that is new, and is not necessarily related to your reasons for ordering such a test. Such information could reveal details about diseases that will only develop in the future, or for which there is no known treatment or cure.
4) The cumulative results of WES testing on many samples may be published in the medical literature. These publications will not include any information that will identify you personally.

Patient Name:	**Patient DOB** *(YYYY/MM/DD):*

Clinical Exome Sequencing – Informed Consent

All sections must be initialed or signed

› Consent Form Clinical Exome Sequencing

Exome sequencing has the potential to detect diseases which the patient may wish to be informed about. Typically these diseases can be categorized as:

1) a predisposition to increased cancer risk;
2) carrier status of recessive diseases;
3) a predisposition to late-onset diseases.

_____ _____
MD Patient

The initials of the physician confirm that **the patient has been informed of the above information**. The patient´s initials confirm whether he/she chooses to be informed about the results of 1) to 3).

› Incidental Findings

As our whole exome sequencing test is analyzing many different genes, there is a potential for the recognition of incidental or secondary findings unrelated to the reason for ordering WES. These findings can provide information that was not anticipated and that are unrelated to the individual's reported clinical features, but are of medical value for patient care.

_____
Patient

Centogene reports mutations of the specified classes or types in the genes listed in the „ACMG Recommendations for Reporting of Incidental Findings" in clinical exome sequencing report. **The patient's initials acknowledge that he/she chooses to receive information regarding genetic results that are unrelated to the specific reason for which my health care provider ordered the test.**

› Future research

_____
Patient

In addition to the most modern technology and continuous training, Centogene´s analytical and research work forms the basis for constant further development. The patient's initials grant Centogene **permission to use any excess samples for future research and development**, while guaranteeing that such samples will always be fully anonymous.

› Private pay patient

_____
Patient

The patient's initials acknowledge that **If an exome test is cancelled** prior to test set-up, Centogene charges a processing fee and will send a cancellation report. Once testing is initiated, the full price of the analysis will be charged.

› LifeLabs

I understand that a DNA specimen will be sent to LifeLabs for genetic testing. My physician has told me about the condition(s) being tested and its genetic basis. I am aware that correct information about the relationships between my family members is important. I agree that my specimen and personal health information may be sent to Centogene AG at their lab in Germany (address below). To ensure accurate testing, I agree that the results of any genetic testing that I have had previously completed by Centogene AG may be shared with LifeLabs. I understand that LifeLabs will contact me for a new specimen if a test result cannot be provided from the original specimen. I agree that a copy of my results will be sent to my ordering physician. I further agree that for any test(s) performed by Centogene AG, a copy of my results will also be sent to LifeLabs. I understand that once the requested test(s) has/have been completed, any remaining sample will be stored at the testing laboratory.

OPTIONAL CONSENT : Please Initial where appropriate

_____ I agree that my de-identified sample may be used for product development or research purposes. I understand that I will not receive any royalties, resultant payments, benefits or rights to products or discoveries.

_____ I do not want my remaining sample to be stored. Please destroy any remaining sample once the final report has been issued.

_____ I have had genetic testing completed in the past by the following laboratories: _____

_____ I agree that Centogene AG and LifeLabs may obtain a copy of these genetic test results from the testing laboratory.

Patient/Substitute Decision Maker: Signature: _____**; Date:** _____

Printed name: _____**; Relationship to person being tested:** _____

› Declaration of Consent for the Performance of a Genetic Analysis

I consent to the carrying out of the genetic investigation(s) indicated on these pages, on myself or the person I am custodian for. I agree to the recording of my personal data, especially my name, date of birth and relationship to other family members and of required medical data, in accordance with data protection regulations. I further agree that the result(s) of the investigation may be recorded for purposes of their transmittance to me or my attending physician in accordance with data protection regulations. The recorded data will not be forwarded to anybody unauthorized. I have been comprehensively informed by my physician of the medical and psychological consequences. I also confirm that I will receive genetic counseling to help me understand the impact and consequences of my diagnostic results.

Patient/Substitute Decision Maker: Signature: _____**; Date:** _____

Printed name: _____**; Relationship to person being tested:** _____

By signing this consent form, I certify that this request is placed in accordance with the legal regulations in our country related to genetic testing.

Healthcare Provider: Signature: _____**; Date:** _____

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WHOLE EXOME SEQUENCING REQUISITION
PARENTAL 1

CENTOGENE
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CONTRACT #	**LL: K012-01/ CML: CEN**	**LifeLabs Demographic Label**
Report to Physician Billing #		
Ordering Physician Name		
Physician Signature:		
Ordering Physician Address & Contact Info:	Address: Tel: Fax:	
Copy to (name & contact info):	Name: Contact:	
Bill to	**Contract # K012-01** (patient does not pay at time of collection)	**Patient Gender:** (M/F)
Patient Name (Last, First):		**Patient DOB:** (YYYY/MM/DD)
Patient Address:	**Patient Health Card:**	**Patient Telephone:**

Please ship all NON-PRENATAL samples to:
LifeLabs · Attn CDS Department • 100 International Boulevard• Toronto ON• M9W6J6

TEST REQUESTED	
☐ **Genetic Test - Blood Sample** 2 x 4mL EDTA	**LL TR # / CML TC#** **4005**
Date Blood Collected (YYYY/MM/DD): _____ **Time Blood Collected** (HH:MM)) :_____ **Collector Name:** _____	

CENTOXOME® PARENTALS
(must accompany "Whole Exome Sequencing – Proband")

Proband Name:	
Parental Information:	Gender: ☐M ☐ F Ethnicity: _____
Sample Type:	☐ ***Blood** (EDTA: 5mL for single gene, 10mL for panel) ☐ **DNA** (single gene:1-10ug, panel 10-100ug) ☐ ***Filter card** (1 card/30 exons: Available by request)

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WHOLE EXOME SEQUENCING REQUISITION
PARENTAL 2

CENTOGENE THE RARE DISEASE COMPANY
Schillingallee 68 · 18057 Rostock Germany

Attention Patient: Please visit your nearest LifeLabs or CML Healthcare Patient Service Centre for sample collection

CONTRACT #	**LL: K012-01/ CML: CEN**	**LifeLabs Demographic Label**
Report to Physician Billing #		
Ordering Physician Name		
Physician Signature:		
Ordering Physician Address & Contact Info:	Address: Tel: Fax:	
Copy to (name & contact info):	Name: Contact:	
Bill to	**Contract # K012-01** (patient does not pay at time of collection)	**Patient Gender:** (M/F)
Patient Name (Last, First):		**Patient DOB:** (YYYY/MM/DD)
Patient Address:	**Patient Health Card:**	**Patient Telephone:**

Please ship all NON-PRENATAL samples to:
LifeLabs · Attn CDS Department • 100 International Boulevard• Toronto ON• M9W6J6

TEST REQUESTED	
☐ **Genetic Test - Blood Sample** 2 x 4mL EDTA	**LL TR # / CML TC#** **4005**
Date Blood Collected (YYYY/MM/DD): _____ **Time Blood Collected** (HH:MM)) :_____ **Collector Name:** _____	

CENTOXOME® PARENTALS
(must accompany "Whole Exome Sequencing – Proband")

Proband Name:	
Parental Information:	Gender: ☐M ☐ F Ethnicity: _____
Sample Type:	☐ ***Blood** (EDTA: 5mL for single gene, 10mL for panel) ☐ **DNA** (single gene:1-10ug, panel 10-100ug) ☐ ***Filter card** (1 card/30 exons: Available by request)

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