CentoNIPT® — Information Sheet

CENTOGENE
THE RARE DISEASE COMPANY

Dear Patient,

Your physician recommends a non-invasive prenatal testing ("**CentoNIPT®**") for you or the patient for whom you are the custodian or legal guardian (hereinafter, "**you**" or "**the Patient**").

CENTOGENE shall only perform the non-invasive prenatal testing. It remains the sole responsibility of the treating physician to interpret the result(s) of such non-invasive prenatal testing and to inform you or the Patient of the results of the genetic testing.

In the following we shall inform you or the Patient about the testing procedure, possible results, and potential risks. You or the Patient may wish to consult with your physician or a genetic counselor before signing the Informed Consent Form.

CentoNIPT screens for some chromosomal disorders in unborn children. During pregnancy, maternal blood contains genetic material, so called cell free DNA (cfDNA), both from the mother as well as from the fetus. DNA encodes the relevant genetic information necessary for the development, function, growth, and reproduction of humans. Chromosomal abnormalities can compromise the developing fetus as a result of incorrect processing of the genetic material in egg or sperm formation and/or during the earliest stages of the fetus' development. These chromosomal abnormalities can significantly affect the health and well-being of the newborn.

The biological material ("**Sample**") required for CentoNIPT is maternal blood.

CentoNIPT screens for:

- **Down syndrome** (Trisomy 21): affects 1 in 1,000 live births
- **Edwards syndrome** (Trisomy 18): affects 1 in 3,000 – 6,000 live births
- **Patau syndrome** (Trisomy 13): affects 1 in every 5,000 live births

If permitted in your country and selected by your or the Patient's physician, CentoNIPT screens for:

- **Turner syndrome** (Monosomy X)
- **Klinefelter syndrome** (XXY)
- **Jacobs syndrome** (XYY)
- **Triple X syndrome** (XXX)

CentoNIPT is also suitable if you or the Patient are/is pregnant with twins. As CentoNIPT includes analysis of the sex chromosomes, the gender of the fetus will be revealed to the laboratory. In case the gender is reported, it may be disclosed by the treating physician according to local laws.

Possible Results and Significance of the Results

CentoNIPT is a screening test – not a diagnostic test. This means, it can predict whether the risk of a genetic condition is high or low. The results will show whether any of the described chromosomal abnormalities have been detected in the fetus. However, CentoNIPT cannot diagnose a genetic condition with 100 percent certainty. A high risk result indicates a substantial increased risk for a specific chromosomal abnormality. On the other hand, a low risk result indicates a significantly decreased risk for the chromosomal abnormalities mentioned. If CentoNIPT is high risk, the treating physician will usually offer you or the Patient an additional analysis to confirm the results and refer you for genetic counselling to discuss the implications and choices available for you and the fetus. Usually, invasive prenatal testing is recommended.

Limitations of CentoNIPT

- CentoNIPT screens for an increased risk for a group of the most common prenatal chromosomal abnormalities. However, CentoNIPT cannot completely exclude the risk for these aneuploidies, other chromosomal abnormalities, or birth defects.
- CentoNIPT is only designed to analyze full chromosome aneuploidies of the fetus after 10 weeks of gestation and is reporting on aneuploidies for chromosomes 21, 18 and 13 in singleton and twin gestations. For singleton gestations, CentoNIPT can optionally screen for sex chromosome aneuploidies (X0, XXX, XXY and XYY).
- In case of organ transplantation from a male donor to the mother, sex chromosome status for the fetus cannot be determined.
- There is a small chance that CentoNIPT may reflect chromosomal changes in the placenta (confined placental mosaicism) or in the mother (chromosomal mosaicism) rather than chromosomal changes in the fetus, as it analyzes both fetal and maternal cfDNA.
- Triple or higher gestations cannot be analyzed by CentoNIPT.
- In case of twin gestations, the detection of chromosome Y indicates that at least one of the fetuses is male; however, the fetal gender of each individual twin cannot be determined by the test. Sex chromosome aneuploidies cannot be analyzed for a twin gestation by CentoNIPT.
- In the case of uncertain or unambiguous results, the further analysis through invasive prenatal testing is usually recommended.
- Low risk results do not eliminate the possibility of chromosomal abnormalities of the tested chromosomes. A low risk result does not eliminate the possibility that the pregnancy has other chromosomal abnormalities (for example microdeletions), genetic conditions or birth defects.
- Results can be confounded by maternal and/or fetal factors like recent maternal blood transfusion, maternal weight, stem cell therapy and others.
- Due to legal restrictions - even if requested - fetal gender will not be included and/or disclosed in the report in selected countries.
- Please note, however that if a sex chromosome aneuploidy is detected and reported, the fetal gender will be revealed and will therefore be explicitly stated on the report, even if not opted for fetal gender to be revealed.

Potential Risks

CentoNIPT is considered non-invasive because it requires drawing blood only from the pregnant woman and does not pose any health risk to the fetus. Despite such, potential risks are: (1) If a blood sample is provided, there can be transient secondary bleeding and pain at the spot of the puncture and, rarely, local allergic reactions; the puncture can also result in bruising. However, these effects usually go away quickly. In very rare cases, the needle can damage a blood vessel or injure a nerve. Nevertheless, the spot of the puncture usually heals with no permanent effects. There are no further health risks associated with CentoNIPT. (2) The communication of the results of the NIPT may result in psychological stress for you or the Patient and family members. (3) If consent has been provided accordingly below, your or the Patient's genetic, and health data, including results of CentoNIPT may be shared with external doctors, scientific institutions, and/or (pharmaceutical) companies for their own scientific (including commercial) research, but solely in de-facto anonymized form. Nevertheless, the risk of re-identification of you or the Patient as a person cannot be completely excluded in theory, due to the uniqueness of genetic information. Such risk increases if and to the extent more information about you or the Patient is publicly available and can be linked to you or the Patient. Therefore, we recommend to handle such information with care, and not to publish in freely accessible databases or elsewhere on the Internet (e.g. for ancestry research), particularly not with any direct information or link to you or the Patient.

Disclaimer

Please note that CentoNIPT is a screening test and not a diagnostic test. Due to limitations in technology and/or current medical knowledge, it is not possible to completely exclude all risks for all possible genetic diseases. Moreover, in some cases, CentoNIPT may incorrectly indicate a high risk of a genetic abnormality when the fetus is actually unaffected (false positive) or may incorrectly not indicate a high risk of a genetic abnormality when the fetus is actually affected (false negative).

If this is not due to an error caused by CENTOGENE, CENTOGENE shall not be responsible for the incomplete, potentially misleading, or incorrect result of CentoNIPT.

Data Protection Notice

CENTOGENE GmbH, Am Strande 7, 18055 Rostock, Germany ("**CENTOGENE**", "**we**" or "**us**") acts as the responsible controller for the collection, use, storage, or disclosure (hereinafter "**processing**") of your or the Patient's personal data. "**Personal data**" means any information relating to an identified or identifiable natural person. If you have any questions on CENTOGENE's data processing or want to make use of your or the Patient's data protection rights, you can contact our data protection officer directly at the address above with the addition: Attn: Data Protection Officer, or via email at dataprivacy@centogene.com.

Data Processing

We collect a Sample and other personal data, including first name, last name, address, date of birth, gender, family relations, ethnicity, nationality, insurance information, patient code number (CGXXXXXXXX), disease, symptoms, and other medical information, including image material, if provided (Art. 6 para. 1 a); Art. 9 para. 2 a) GDPR), which will then be processed in our databank. The Sample is analyzed using state-of-the-art scientific methods and the extracted data is processed with the collected data in our databank. We then provide the results – containing genetic and health data of you or the Patient - to your or the Patient's treating physician. If you or the Patient consent to further use of your or the Patient's personal data as set our below, your or the Patient's data will be de-facto anonymized, which means that it will not be possible to reidentify you.

Data Storage Period

We archive the Sample for up to 1 year and the personal data for up to 10 years after the result has been reported. We delete or anonymize the personal data and destroy the biological material thereafter if this has not already happened. You or the Patient also have / has the option to agree to further use of your or the Patient's personal data for scientific (including commercial) research purposes. The data may be of scientific importance when improving diagnosis and treatment of rare diseases, including scientific publications. Insofar you or the Patient consented to the further use of personal data, personal data will be stored for up to 20 years after the last result has been reported and deleted or anonymized thereafter.

Recipients of Personal Data

In principle, we process personal data ourselves. Any transfer of personal data to a third party only takes place (1) with either explicit consent, (2) in order to fulfil a legal obligation or (3) if such transfer is permitted by law. In this regard, please be informed as follows:

- We use third party services, e.g. IT-service providers that maintain our systems or data centers which host such systems. Such third-party services are considered as data processors under GDPR. These data processors have been carefully selected by us, are contractually bound to comply with data protection laws, are subject to our instructions and regular monitoring and are only allowed to use the data they receive to fulfil their contractual obligations. We always agree on GDPR-compliant data processing agreements with such data processors.
- If consent has been provided accordingly below, we may provide biochemical, genetic and health data, including results of CentoNIPT – solely in de-facto anonymized form – to external physicians, scientific institutions and / or (pharmaceutical) companies for their own scientific (including commercial) research.
- We provide the results of CentoNIPT and the raw data to the treating physician and / or eventually to the requesting laboratory and may provide the results of CentoNIPT to the health care professionals who are involved in your or the Patient's medical counseling and / or clinical care.

International Data Transfer

The Sample will be analyzed in Germany. In principle, we process personal data solely within Germany, the European Union, and the European Economic Area ("**EEA**"), where GDPR-provisions apply. If the treating physician, and other recipients are located in a so-called third country outside the EEA where GDPR provisions do not apply, your or the Patient's personal data shall be transferred to this third country. Such transfer will only take place with your or the Patient's consent. If a data processor is based outside the EEA, we may transfer the personal data to such third country, provided that, either (1) the European Commission has decided that this third country already provides an adequate level of data protection or (2) we establish appropriate data protection safeguards with the data processor; e.g. by concluding so-called "standard contractual clauses", respectively including supplemental clauses containing additional safeguards. In such cases, you or the Patient have / has a right to request a copy of these "standard contractual clauses". To do so, please contact our data protection officer.

Data Protection Rights Under the EU General Data Protection Regulation ("GDPR")

- Right to withdraw your consent with regard to data processing
- Right of access
- Right to data portability
- Right to rectification
- Right to erasure
- Right to restriction of processing
- **Right to object**
- Right to lodge a complaint with a supervisory authority

Additional Rights Under the German Genetic Diagnostics Act (Gendiagnostikgesetz)

- Right to withdraw your consent to CentoNIPT (until such has been performed)
- Right to request destruction of the Sample
- Until the moment you or the Patient has been given the results of CentoNIPT, the right not to be informed about such results in full or in part (right not to know); and the right to request destruction of all such results

To exercise the rights, please contact our data protection officer.

With my signature below, I confirm or confirm on behalf the Patient for whom I am the custodian or legal guardian (hereinafter, "**I**" or "**the Patient**") that I or the Patient have / has received, read, and understood the preceding written explanation about the non-invasive prenatal testing. I or the Patient have / has been adequately informed regarding the purpose, scope, type and significance of such analysis, possible results, and possible risks. The responsible physician has informed me or the Patient about possible prevention / treatment measures of any possible disease. Furthermore, I confirm that I have had sufficient opportunities to ask questions and such questions were answered in an understandable manner and to my or the Patient's full satisfaction.

Consent to the Non-Invasive Prenatal Testing and Related Data Processing

By signing this Informed Consent Form, I consent or consent on behalf the Patient for whom I am the custodian or legal guardian

(1) to non-invasive prenatal testing ("**CentoNIPT**") of my or the Patient's biological material ("**Sample**") by CENTOGENE GmbH, Am Strande 7, 18055 Rostock, Germany ("**CENTOGENE**") to screen for chromosomal abnormalities of the fetus as specified in the Information Sheet; (2) to any necessary processing of my or the Patient's personal data to perform such CentoNIPT as specified in the Information Sheet; (3) to provide the results of CentoNIPT as well as the fetal gender (if applicable) to the treating physician and to be informed by the treating physician of the results of CentoNIPT and the fetal gender (if applicable); (4) to provide the results of the CentoNIPT to health care professionals who are involved in my or the Patient's medical counseling and / or clinical care, if so requested by the treating physician; (5) to provide the results of CentoNIPT to the requesting laboratory, as instructed by the treating physician; (6) to provide raw data of CentoNIPT, upon request, to the treating physician and / or the requesting laboratory; and (7) to store the Sample for up to 1 year and the personal data for up to 10 years after CENTOGENE has reported the result and (8) to anonymize the personal data thereafter.

Furthermore – if the following recipients are located in a so-called third country outside the European Economic Area, where GDPR provisions do not apply – I consent to the transfer of my or the Patient's personal data to this third country, in particular (1) to provide the results of CentoNIPT and the raw data to the treating physician and / or the requesting laboratory; and (2) to provide the results of CentoNIPT to the health care professionals who are involved in my or the Patient's medical counseling and / or clinical care. I acknowledge that such third country may not provide a level of data protection equivalent to the GDPR and may grant fewer or less enforceable data protection rights and no independent data protection supervisory authority to assist in exercising these rights.

Optional Consent to Further Use of the Personal Data

I understand that my or the Patient's personal data may enable CENTOGENE to develop and improve diagnostic methods and therapeutic solutions for genetic diseases in general. This may help myself, my family members, and other patients in the future. However, such consent is voluntary and not necessary to conduct CentoNIPT as specified above.

I acknowledge that I or the Patient will not receive any compensation for the provision of personal data. I waive any claims for compensation, royalties, or other financial benefits that may arise from scientific (including commercial) research usage of the personal data.

(1) I consent to the usage of my or the Patient's personal data by CENTOGENE for scientific (including commercial) research, which focuses on the cause, early detection and / or treatment of rare diseases in general. I acknowledge that the personal data will be used in the interest of the greatest possible benefit to the general public for research which aims to improve the prevention, detection and treatment of rare diseases. Such includes but is not limited to disease areas such as metabolic disorders, neurodegenerative disorders, cardiac disorders, and malformations as well as to diseases and genetic relationships that are still unknown today. As in any research on rare diseases – particularly due to the latest findings in genetic diagnostics – it is usually not possible to predict in detail which research questions and matters will be addressed in the future. Therefore, the specific research purpose cannot be detailed herein, and the data may also be used for medical research projects that cannot be foreseen today.

(2) I consent that CENTOGENE shares my or the Patient's biochemical, genetic, and health data, including results of CentoNIPT – solely in de-facto anonymized form – with external doctors, scientific institutions and / or (pharmaceutical) companies for their own scientific (including commercial) research. I acknowledge that "de-facto anonymized" means that the data available at CENTOGENE is altered in such a way, including redaction and removal of any pseudonyms, that re-identification of the Patient as a person for any further recipient of the data is practically impossible. However, the confidentiality risks described in the Information Sheet persist.

(3) I consent that CENTOGENE stores my or the Patient's personal data for 20 years after the last result has been reported for further scientific (including commercial) research, which focuses on the cause, early detection and / or treatment of rare diseases in general.

☐ **Yes**

I understand that this consent is voluntary and is valid until such time as I choose to withdraw the consent. The consent with regard to (1) CentoNIPT and / or the disclosure of the fetal gender can be withdrawn until such has been performed; and (2) to the processing of the personal data can be withdrawn at any time. Furthermore, the destruction of the Sample can be requested; in each case with effect for the future.

Until the moment the results of CentoNIPT and / or the fetal gender have been provided to me or the Patient, I understand I have the right (1) not to be informed about such results (so called right not to know); and (2) to request the destruction of all such results. To withdraw the consent and / or to exercise the rights, I may contact CENTOGENE's data protection officer.

Date	Name and date of birth (DD.MM.YYYY) of the Patient	Signature of the Patient, and / or custodian / legal guardian

Notice to the treating physician

The applicable law requires informed consent from the patient to be able to perform a non-invasive prenatal testing. Please ask your patient to sign the informed consent form so that the commissioned service can be provided. Alternatively, please confirm with your signature that the patient has consented accordingly and that you have such consent on file. This consent must be provided upon request. Subsequently, please send the completed and signed informed consent form together with the information sheet and sample(s) to CENTOGENE. If a sex chromosome aneuploidy is detected and reported, the fetal gender will be revealed and will therefore be explicitly stated on the report, even if not opted for fetal gender to be revealed. If reporting the fetal gender is not desired, reporting of both, fetal gender and sex chromosome abnormalities must be opted out.

Physician's Confirmation

I acknowledge that (1) the consent as shown above has been declared by the Patient and/or the Patient's custodian/legal guardian , (2) I have the Patient's and/or custodian's/legal guardian's signature on file if it is not shown above, (3) the Patient and/or custodian/legal guardian is capable of giving consent, (4) all questions of the Patient and/or custodian/legal guardian have been answered, (5) the Patient and/or custodian/legal guardian had the necessary time to consider the decision, and (6) the Patient and/or custodian/legal guardian until now have not exercised the right not to be informed of genetic testing results. I understand that (1) the Patient and/or custodian/legal guardian may exercise any of the rights specified in the Information Sheet and (2) I shall forward such requests to CENTOGENE without undue delay.

Date	Name of the treating physician	Signature of the treating physician