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CLA_V004 1.0

Non-invasive genetic analysis to understand pregnancy loss

INSTRUCTIONS FOR USE

CLARITY is a non-invasive genetic laboratory developed test (LDT) performed on a **blood sample** taken from a woman after pregnancy loss. The analysis is based on **cell-free DNA** (cfDNA), which consists of circulating DNA fragments originating from both the pregnant individual and the miscarried pregnancy. The test is intended to identify chromosomal abnormalities that may be associated with the pregnancy loss. As the analysed cfDNA contains both maternal and fetal components, the test may also detect maternal chromosomal copy number variations that could be associated with the pregnancy outcome.

The CLARITY test has been validated to detect the following chromosomal conditions using genome-wide analysis:

- **Autosomal aneuploidies** involving chromosomes 1–22
- **Sex chromosome aneuploidies** (e.g. Turner syndrome (45,X), Klinefelter syndrome (47,XXY), Jacobs syndrome (47,XYY), and trisomy X (47,XXX))
- **Fetal chromosomal sex**

The CLARITY test is validated for use **from 6 weeks of gestation** onwards. The test is intended for use by qualified healthcare professionals. It is a qualitative test that determines the presence or absence of the analysed chromosomal abnormalities.

METHODS

For the CLARITY test, cell-free DNA (cfDNA) is extracted from a maternal blood sample and converted into a sequencing library using the Focus Plus laboratory method. This method includes enrichment of fetal-origin cfDNA prior to sequencing, thereby increasing the fetal fraction and enhancing the test's analytical sensitivity. Sequencing is performed on an Illumina platform. CLARITY applies a genome-wide analysis approach. Sequencing data are generated across all 23 chromosome pairs. During bioinformatic analysis, sequencing reads are aligned to a reference genome, and their genomic distribution is evaluated. Based on the relative representation of reads across the genome, risk scores are calculated. In addition, fetal chromosomal sex is determined.

QUALITY PARAMETERS

The analytical performance of the test has been evaluated for the following categories:

Sensitivity:

- Autosomal aneuploidies: 95%
- Sex chromosome aneuploidies: >99%
- Fetal chromosomal sex determination: >99%

Specificity (all categories): ≥85%

These performance characteristics are based on validation studies conducted under controlled conditions and may vary depending on sample quality, fetal fraction, and other pre-analytical and analytical factors.

CLARITY kit

The CLARITY kit includes the following components:

- 10 mL blood collection tube (Streck Cell-Free DNA BCT)
- Absorbent sleeve for the blood collection tube
- Plastic transport bag
- Shipping box
- Quick guide with a link to the Instruction of Use (QR code)
- Patient consent form

The kit must be stored at room temperature. The shelf life of the CLARITY kit is indicated on both the blood collection tube and the shipping box. Kits that have exceeded their shelf life must not be used and should be returned to the laboratory.

!!! The blood collection tube is made of glass and may break. If the tube breaks, follow your institution's safety procedures. Damaged tubes or caps must not be used, even if they appear sterile.

ORDERING

It is recommended that the CLARITY test be ordered through the secure electronic form available at **labor.ut.ee**
For electronic ordering, Celvia CC provides each clinic with a unique ordering code after a service contract has been signed.

Alternatively, the CLARITY test may be ordered using the **Patient consent form** included in the kit. The document must be completed and signed **before** the patient's blood sample is collected.

BLOOD SAMPLING

The CLARITY test requires a venous blood sample from a woman who has recently experienced a miscarriage. The retained pregnancy tissue must still be present in the uterus at the time of blood collection. Blood must be drawn into the blood collection tube supplied in the kit and the tube must be filled to at least 80%. If sample collection is unsuccessful (e.g., insufficient blood volume), a new kit must be used. No additional consumables are provided. Blood collection should follow the clinic's standard procedures or the CLSI GP41 guideline. If multiple tubes are collected during the same venipuncture, an **EDTA tube should be drawn prior to the CLARITY tube, and the use of heparin-containing tubes immediately prior to the CLARITY tube should be avoided**.

After collection, the blood must be thoroughly mixed with the stabilising agent in the blood collection tube by gently inverting the tube 180° at least ten times. Additional instructions can be found inside the shipping box. The filled tube should be sent to the laboratory as soon as possible. The transportation temperature range is defined on the kit shipping box.

The blood sample must be transported to the Celvia CC medical laboratory by courier.

Quick guide for packaging and shipment

1. Prepare the sample
    - Place the filled blood collection tube into the absorbent sleeve.
    - Seal the tube inside the plastic transport bag.
    - Place the sealed bag into the black shipping box.
2. Include documentation
    - Add one signed copy of the patient consent form to the black shipping box.
3. Arrange courier pickup
    - Order the courier according to the instructions printed inside the shipping box.
4. Close the shipment
    - Secure the shipping box using the rubber bands provided.

RESULTS

Test results are transmitted electronically to the healthcare provider who ordered the analysis. Both negative and positive results should be communicated to the patient by a qualified healthcare professional or a clinical geneticist, and appropriate counselling should be provided. Together with the patient, the healthcare provider will determine the appropriate next steps based on the test results. The possible outcomes of the CLARITY test are described below.

Positive result

One or more chromosomal abnormalities have been identified. These findings may represent a possible cause of the miscarriage. The abnormality may originate from the retained fetal tissue or, in some cases, from maternal chromosomal alterations. If a maternal origin finding is suspected, it will be indicated in the report.

Negative result

No chromosomal abnormalities were detected in the analysed sample. A negative result does not exclude a genetic cause of the miscarriage, as some chromosomal or genetic changes may fall outside the scope of the test or below its technological detection limits.

Non-informative result

A result may not be reported for one or more of the following reasons:

- The blood collection tube was filled to less than 80% of the required volume.
- The gestational age is less than 6 weeks.
- The transport time exceeded 14 days between blood collection and registered at the Celvia CC laboratory.
- The blood collection tube was damaged upon arrival at the laboratory.
- The test data contained excessive background noise (e.g. high standard deviation), preventing reliable assessment of chromosomal abnormalities. This may be related to the specimen itself or to transport conditions.
- Errors in sample or consent form identification (e.g. incorrect coding) prevented reliable linkage of the results to a specific patient.

The overall probability of a non-informative result is low (<1%).

LIMITATIONS

The CLARITY test detects the most frequent chromosomal abnormalities associated with gestational loss; however, it does not identify all genetic disorders or all possible chromosomal changes. Because the method relies on whole-genome cfDNA sequencing, certain abnormalities cannot be reliably detected. Therefore, the possibility of both false-negative and false-positive results cannot be completely excluded.

The test is not designed or validated to detect:

- Triploidy or tetraploidy
- Monogenic (single-gene) disorders or point mutations
- Small copy number variances (CNV)
- Low-level or tissue-confined mosaic chromosomal abnormalities
- Balanced structural chromosomal abnormalities (e.g. balanced translocations or inversions)
- Uniparental disomy

A negative test result (i.e. no chromosomal abnormality detected) reflects only the chromosomal status of the analysed cell-free DNA and does not exclude other genetic or non-genetic causes of pregnancy loss. The CLARITY test does not provide information on fetal structural development and does not assess causes of pregnancy loss related to uterine, placental, or maternal–fetal interface dysfunction.