Identification label patient

FORM FOR OBTAINING INFORMED CONSENT

FOR NON-INVASIVE PRENATAL SCREENING WITH COMBINED TESTING

Pursuant to Art. 1, Paragraph 3, Law 219/2017, "Every person has the right to know their health conditions and to be informed in a comprehensive, up-to-date, and understandable manner."

Dear Sir/Madam	Surname:_____ Name:_____ Place of birth:_____ Date of birth:____/____/_____

You have come to this facility to undergo non-invasive prenatal screening with the Combined Test, in accordance with the prenatal screening program of the Lombardy Region.

Before undergoing non-invasive prenatal screening, it is essential that you are informed and fully understand what the test involves, its opportunities, limitations, and possible alternatives, as well as its ethical and legal implications, in order to make an informed and responsible choice (whether or not to take the test, what to do when you receive the results).

This information sheet contains the essential explanations, which will be supplemented by a consultation with the doctor responsible for performing the test, both before and after the test. If any information is unclear, you can ask the doctor for further details during the pre-test consultation.

Proposed treatment: COMBINED TEST

The vast majority of pregnancies result in the birth of a healthy baby. However, there is a small chance that the fetus may have chromosomal abnormalities, the most common of which are trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), and trisomy 13 (Patau syndrome).

The only way to know for sure whether the fetus has these or other chromosomal diseases is to undergo an invasive diagnostic test to determine the fetal karyotype, such as villocentesis (which can be performed from the 11th week of gestation) and amniocentesis (which can be performed from the 15th week of gestation). these carry a risk of miscarriage linked to the procedure of approximately 0.2-0.5% more than the natural miscarriage rate of 1-2%.

Invasive prenatal diagnosis is therefore reserved for cases where the probability of the fetus having problems is significantly higher than in the general population. It is also worth remembering that chromosome analysis after an invasive prenatal test does not rule out all genetic diseases and rare syndromes.

Based on these considerations, screening tests (e.g., combined tests) are generally used. Although these tests do not provide certainty regarding the diagnosis of trisomy 21 or other rarer chromosomal defects (trisomy 13 and 18), they do allow the specific risk of each woman having a child affected by these syndromes to be calculated with reasonable accuracy.

What is the Combined Test?

It is a screening test performed during the first trimester of pregnancy that provides a personalized risk assessment for chromosomal abnormalities, such as trisomy 21, trisomy 18, and trisomy 13. *It correlates the basic risk linked to* ***maternal age*** *alone with the risk obtained from ultrasound* ***measurement of fetal nuchal translucency*** *and maternal blood testing for* ***two placental hormones, free-β-HCG and PAPP-A.***

Therefore, between the **11th and 13.6th** weeks of pregnancy, an ultrasound scan is performed, during which the profile of the fetal face is visualized and the **nuchal translucency** is measured, which appears as a collection of fluid visible by ultrasound as an echo-free (black) space behind the fetal neck. Nuchal translucency can be measured by ultrasound in the vast majority of fetuses, but it is thickened, and therefore above normal limits, in approximately 75-80% of fetuses with trisomy 21; it is also increased in a high percentage of fetuses with other chromosomal abnormalities or genetic syndromes.

In the days leading up to the ultrasound, a blood sample is taken from the mother to measure the concentrations of two substances produced by the placenta, the free fraction of beta-HCG and PAPP-A, two hormones that are often altered in pregnancies affected by trisomies 21, 18, and 13.

The first trimester combined test is not a definitive diagnostic test; rather, it expresses **a probability**: a higher probability does not mean that the baby is definitely affected, just as a lower probability does not mean that the baby is definitely free of the condition in question. The first trimester combined test can identify about 90% of fetuses affected by trisomy 21 and most of those with trisomy 18 and 13, with a false positive risk of around 5% and a false positive risk of 10% for trisomy 21.

Therefore, using an internationally accredited computer program, the combination of maternal age, nuchal translucency, and maternal blood test results will be used to calculate the **personalized probability that the fetus is affected by trisomy 21, 18, or 13**, and this can be compared with the probability linked to the mother's age alone, **defining the risk** at the end of the test as **low, intermediate, or high.**

This is not a routine test, so you are free to choose whether or not to undergo it: ***the Regional Health System (SSR) offers only the Combined Test free of charge as a first-line test, while fetal DNA testing in the maternal circulation (cf DNA/NIPT) is only offered as a second-line test in cases of increased risk.***

What further tests are required in cases of intermediate/high risk?

The screening report is always delivered personally to the patient by the doctor who performs the ultrasound and processes the data: through a **post-test consultation**, they will communicate the definitive risk and define any further tests that may be required.

The result of the combined test is expressed as a probability of disease risk, which can be defined as:

Low Risk (less than one in a thousand, **<1 in 1000**), no further investigation is indicated.
Intermediate Risk (probability between 301 and 1000), in this case the pregnant woman will be summoned by the center where the combined test was performed for an interview in which a second screening test will be offered free of charge through SSR with the search for fetal DNA in the maternal circulation (cf DNA/NIPT), which has a much higher sensitivity for trisomies 21, 18, and 13 compared to the combined test (sensitivity for trisomy 21 of 99.9% with false negatives <1%).
High risk (greater than 1 in 300 probability) in this case, the pregnant woman will be summoned to the Prenatal Diagnosis Center of ASST Bergamo Est, where a new fetal ultrasound will be performed and a consultation will be held to discuss the results and decide on further tests such as diagnostic testing (amniocentesis or villocentesis) or a second screening test to search for fetal DNA in the maternal circulation (cf DNA/NIPT).

Patients who have achieved pregnancy through **assisted reproductive technology** (ART) are required to inform healthcare personnel because this information is included in the risk calculation.

Patients who have achieved pregnancy through **egg donation or frozen eggs** must provide certification (preferably from the center where fertilization was performed) attesting to the age of the donor or the date of egg freezing. The screening test assessment is based on the baseline risk related to the age of the woman who donated the egg.

What are the quality guarantees for the Combined Test?

The ASST Bergamo Est Analysis Laboratories are accredited by national and international control bodies. The gynecologists and ultrasound technicians who perform the examination are subject to annual checks on their case history and the quality of their work, in accordance with the guidelines of the Italian National Institute of Health.
In a small percentage of cases, the characteristics of the maternal tissues and/or the fetal position may prevent clear visualization of the fetal structures of interest using transabdominal ultrasound. In these cases, transvaginal ultrasound may be required and/or the examination may be suspended and resumed after a few minutes or a few days. Despite these attempts, there are rare cases in which it is technically impossible to complete the examination and provide the screening test results.

Patient Questions:

_____

Clinician responses:

_____

Information on the risks in case of refusal or delay in performing the test:

If you **refuse** the combined test, you can choose another prenatal screening or diagnostic option outside the SSR program, or you can choose not to perform any screening tests for aneuploidy of chromosomes 13, 18, and 21.
If you have not undergone the combined test and are **beyond the gestational age limit** for its execution (fetal crown-rump length 45-84 mm), the quadruple test may be offered for risk assessment.
The QUADRUPLE TEST (QUAD-TEST) is a screening test applicable in the second trimester of pregnancy. It can be performed between the 15th and 19th weeks of gestation. The levels of AFP (alpha-fetoprotein), hCG (human chorionic gonadotropin), uE3 (free estriol), and inhibin A are measured in the maternal blood sample.
The ASST Spedali Civili di Brescia Laboratory has been identified as the regional reference laboratory for performing the quadruple test; the attending physician will contact the facility if necessary.
This test may be followed by further investigation with CF-DNA or invasive diagnostics depending on the level of risk identified.

Diagnostic/therapeutic alternatives:

There is another screening test for aneuploidies of chromosomes 13, 18, and 21, which consists of FETAL DNA SEARCH IN THE MATERNAL CIRCULATION (CF DNA/NIPT): this test is preferably performed in the first trimester of pregnancy, after the 10th week of gestation, and allows the probability of the fetus having a genetic abnormality to be identified through a blood sample for the analysis of free DNA present in the maternal plasma of placental origin.
Among the screening tests available, NIPT is the one with the highest sensitivity; in fact, the probability of identifying a fetus affected by one of the three trisomies is around 99% with a false negative rate of <1%.
This is not a diagnostic test either, so in the event of a high-risk result, confirmation of disease in the fetus must be performed with an invasive test: villocentesis or amniocentesis.

NB ***This highly sensitive screening test is not currently provided by the SSR as a first-choice test, but only as a second-line screening test in the event of an intermediate/high-risk Combined Test.***

Additional information:
Please note that ASST Bergamo Est is part of the university training network, therefore it is possible for doctors undergoing specialist training to collaborate/actively participate under the supervision of a permanent doctor (tutor).

SIGNING OF CONSENT/DISSENT – CAPABLE PERSON

I, the undersigned	Surname: _____ Name:_____ Place of birth:_____ Date of birth: _____/_____/_____

➢ **Check the selected option:**

□ I freely and voluntarily agree, having understood the situation explained to me, to undergo the following MEDICAL PROCEDURE(S):

□ NON-INVASIVE PRENATAL SCREENING WITH COMBINED TESTING, the details of which were explained during the information session and summarized in this document.

□ I FREELY AND VOLUNTARILY AGREE to undergo the treatments proposed by the doctor/team, about which I **do not wish to be informed.**

□ I **DO NOT AGREE** to undergo the proposed treatments, aware of the **risks** that **refusal of treatment** may entail, namely (specify):_____

□ I **DELEGATE** AS A FAMILY MEMBER OR PERSON OF MY TRUST RESPONSIBLE FOR EXPRESSING CONSENT ON MY BEHALF Mr./Ms._____born_____ on_____

(Fill in the appropriate form SIGNATURE OF CONSENT EXPRESSED BY THE DELEGATE)

□ I also DECLARE that I am aware of the possibility of REVOKING this consent/refusal at any time during treatment.

Signature of the person receiving assistance			
Doctor's first and last name Tax ID number or registration number or stamp		**Signature:**	
Date and time of consent/dissent acquisition	Date:____/____/_____ Time:_____:_____		
IN THE EVENT THAT THE PERSON BEING ASSISTED IS PHYSICALLY UNABLE TO SIGN			
First name, last name, date and place of birth (witness 1)		**Signature**	
First name, last name, date and place of birth (witness 2)		**Signature**	

SECTION RESERVED FOR THE CULTURAL MEDIATOR (if present)

I declare that I was present at the signing of the consent form and at the informative interview that preceded it, during which I acted as a mediator, faithfully translating the contents of the interview. My translation work also involved putting the questions asked by the person being assisted and/or their family members to the doctors and faithfully translating their answers, as well as reading this document.

First name Last name, date and place of birth - Cultural mediator		**Signature**	
Date and time of consent acquisition	Date:____/____/_____ Time:_____:_____		

SIGNING OF CONSENT/DISSENT DELEGATE/GUARDIAN/SUPPORT ADMINISTRATOR	
I, the undersigned	Surname: _____ Name:_____ Place of Birth:_____ Date of birth: _____/_____/_____
As	❑ Delegate ❑ Guardian (decree no.: _____) Support administrator with powers of ASSISTANCE in the healthcare sector (decree no: _____) ❑ Support administrator with powers of EXCLUSIVE REPRESENTATION in the healthcare sector (decree no:_____)

After consulting with the interested party where possible

Please tick the chosen option:

❑ **I ACCEPT,** freely, spontaneously, and in full awareness, having taken note of the situation described, that Mr./Ms. Surname _____First name:_____be subjected to the following

❑ NON-INVASIVE PRENATAL SCREENING WITH COMBINED TEST the details of which were explained during the information session and summarized in this document

❑ **I DO NOT ACCEPT**, aware of the **risks** that **refusal of treatment** may entail, that Mr./Ms. Surname:_____ Name:_____ undergo the following MEDICAL PROCEDURE:

_____

_____

(INDICATE MEDICAL PROCEDURE - LOCATION - LATERALITY)

the details of which were explained during the informative interview and summarized in this document, and of the possibility, in the event of disagreement, of appealing to the guardianship judge for a decision (pursuant to Paragraph 5, Art. 3).

❑ I also **DECLARE** that I am aware of the possibility of REVOKING this consent/dissent at any time during treatment.

Signature of the person receiving assistance			
Doctor's first and last name Tax ID number or registration number or stamp		**Signature**	
Date and time of consent/dissent acquisition	Date:____/____/_____ Time:_____:_____		

SECTION RESERVED FOR THE CULTURAL MEDIATOR (if present)

I declare that I was present at the signing of the consent form and at the informative interview that preceded it, during which I acted as a mediator, faithfully translating the contents of the interview. My translation work also involved putting the questions asked by the person being assisted and/or their family members to the doctors and faithfully translating their answers, as well as reading this document.

First name Last name, date and place of birth - Cultural mediator		**Signature**	
Date and time of consent acquisition	Date:____/____/_____ Time:_____:_____		

In case of withdrawal of consent, please fill out the appropriate form.