harmony
PRENATAL TEST

cenata
safe method. secure result.

Harmony® Prenatal Test
Educational Brochure

Cenata GmbH

Educational Brochure Harmony® Prenatal Test

Dear mother-to-be, dear family,

you received a recommendation to perform the „Harmony® Prenatal Test" in order to screen for the most common chromosomal disorders (aneuploidies) in your unborn child. In this situation, questions may arise, which we try to answer with this educational brochure.

If you have any further questions, please contact your doctor or the Cenata team.

What is a chromosomal disorder?

The genetic information in the human body is organised in the form of 23 pairs of chromosomes. In a numerical chromosomal disorder, chromosomes are missing, or extra copies of one or several chromosomes are present. E.g. in case of a trisomy, a particular chromosome occurs in triplicate, instead of - as usual - in duplicate.

Trisomy 21 („Down's syndrome") is the most common chromosomal disorder in humans. It is usually associated with a mostly moderate mental disability and can also cause other diseases, e.g. congenital heart defects. Trisomy 21 occurs in approximately one of 500 pregnancies, highly dependent on the age of the mother. The risk for carrying a child with trisomy 21 is about 1 of 1050 for a 20-year-old woman but already 1 of 100 if the woman is 40 years old [1].

Trisomy 18 causes the „Edwards syndrome", which is associated with a high miscarriage rate (only about one in six children diagnosed with trisomy 18 in the 13th week of gestation is born alive). Children born with the Edwards syndrome are typically severely disabled and usually suffer from multiple diseases simultaneously. They typically have a life expectancy of only a few months. Edwards syndrome occurs in approximately one of 5000 newborns [2].

Trisomy 13 causes the „Patau syndrome", which is also associated with a high miscarriage rate. Children born with trisomy 13 usually suffer from severe congenital heart disease and other disorders. They rarely survive the first year after birth. According to estimates, trisomy 13 occurs in one of 16.000 newborns, whereas a higher maternal age also increases the risk of this trisomy [3].

An additional or missing copy of the X or Y chromosome causes certain disorders, e.g. monosomy X (Turner syndrome) or Klinefelter syndrome. There is a high variability in expression of these **sex chromosomal disorders** [4]. monosomy X has only one X chromosome (instead of two X chromosomes or one X and one Y chromosome) [5]. Usually, this disorder is associated with normal development of intelligence, but a premature termination of the pregnancy occurs quite frequently. Later in life, children with monosomy X are commonly of short stature and have certain physical characteristics.

By contrast, patients with an additional X chromosome develop largely normally. However, some disorders (e.g. Klinefelter syndrome [6]) are associated with infertility. This also applies to women with monosomy X.

A diagnosis with nearly one hundred percent of certainty of whether a fetal chromosomal disorder is present or not is only possible by karyotyping after amniocentesis or after a biopsy of the placenta (chorionic villus sampling). These methods are referred to as "invasive" because they require a puncture of the amniotic sac or the placenta with a needle. Correspondingly, these procedures can result in the loss of the unborn child, statistically in about every thousandth intervention.

The Harmony® Prenatal Test

During pregnancy, DNA fragments of the placenta are released into maternal blood. The Harmony® Test is a sophisticated screening test that examines these cell free DNA fragments from the mother's blood and determines the risk of the unborn child for having a trisomy 21, trisomy 18, trisomy 13 or a disorder of the sex chromosomes (X/Y).

The Harmony® Test is validated for use in single and twin pregnancies. A risk analysis with the Harmony® Test is possible without limitations after fertility treatment, in-vitro fertilization with own oocytes, and after an egg donation also.

The Harmony® Test can be performed from gestational week 10+0 onward. Two blood tubes are collected and serve as test material, each of them filled with 8.5mL of venous blood of the mother. Shortly prior to taking blood for the Harmony® Test, an ultrasound examination should be performed. This is important to determine whether you have a singleton or twin pregnancy and to confirm the vitality of the unborn child /children. Moreover, it is necessary that you have received comprehensive genetic counseling by your doctor regarding the Harmony® Test and are aware of and understand the possibilities, limitations, and risks of the examination. After the laboratory analysis of the Harmony® Test is completed, the result will be sent to the doctor who submitted it. He will inform you about the test result together with genetic counseling.

The Harmony® Test is a non-invasive prenatal test (NIPT). This means that there is no need for an invasive procedure to obtain amniotic fluid or placental material. Accordingly, there is no risk of miscarriage due to surgery. A NIPT does not recognize chromosomal disorders with one hundred percent of certainty. Some cases of trisomy and other chromosomal disorders may be overlooked, although this is rare. Even false positive results are possible, which is also rare. If a clear diagnosis is required, an **amniotic fluid examination (amniocentesis)** followed by chromosomal analysis must be carried out. In this invasive method, which can be performed from the 16th gestational week onward, fetal cells from the amniotic fluid are examined for chromosomal disorders.

Before the 16th week of gestation, **chorionic villus sampling** (CVS, removal of tissue from the placenta) with subsequent chromosomal analysis can be performed. However, the chromosomes of the cells of the placenta may in a few cases differ from the fetal cells, which is why - as in the case of the Harmony® Test - a finding that does not reflect the actual chromosomal set of the unborn child can occur in a few cases.

What does the Harmony® Test determine?

The Harmony® Test is an advanced screening test that determines the risk of the unborn child suffering from any of the following chromosomal disorders:

- Trisomy 21 (Down syndrome)
- Trisomy 18 (Edwards syndrome)
- Trisomy 13 (Patau syndrome)
- Sex chromosomal disorders (XO, XXY, XXX, XYY, XXYY)

If desired, the fetal sex can be determined in addition. According to the German Genetic Diagnostic Act, the fetal sex may only be communicated to you after the gestational week 14+0.

How safe and accurate is the Harmony® Test?

The Harmony® Test has been clinically validated in numerous studies involving more than 148,000 pregnant women [7-11,13,21-74,77]. The following overview summarises the test's performance data of the most important studies (as of August 2020) [8, 13]:

Chromosomal disorder	Detection rate	False positive rate
Trisomy 21	99.3%	< 0.1%
Trisomy 18	97.4%	< 0.1%
Trisomy 13	93.8%	< 0.1%
Sex chromosomal disorders	94.6%	0.14%

As mentioned previously, a NIPT, such as the Harmony® Test, is not a diagnostic test. There is a possibility of false positive and false negative results. A false positive result means that the Harmony® Test indicates a high risk for a chromosomal disorder, even though the unborn child is healthy. Even if the likelihood of a false positive result is low, a high risk outcome for a chromosomal disorder should always be confirmed by invasive examination. A false negative result means that a trisomy or sex chromosomal disorder was analysed in the test but has not been detected.

What to expect from your results

A risk of less than 1% is defined as a low probability of a chromosomal disorder; a risk greater than 1% is defined as a high probability. Most pregnant women receive a very low risk (below 1 in 10,000) as a result of the Harmony® Test. This indicates that the unborn child is unlikely to have any of the investigated chromosomal disorders. The negative predictive value (NPV) of the Harmony® Test is higher than 99.9%. This means that more than 99.9% of the low-risk results are correct and the child does not suffer from any of the investigated chromosomal disorders. However, a low risk does not completely exclude a chromosomal or genetic disorder of the child.

A high risk (>1%) for a chromosomal abnormality in the Harmony® Test is not a diagnosis. It indicates that there is a high risk that the child does actually carry this chromosomal disorder. According to the recommendation of several medical societies, such a high risk result must be further examined with a diagnostic (invasive) method, i.e. an amniotic fluid examination, before a consequence can be drawn. The positive predictive value (PPV) of the Harmony® Test is almost 80% for trisomy 21. This means that almost 80% of high-risk outcomes are correct, and the child is actually suffering from one of the investigated chromosomal disorders. Your individual PPV depends on your age and on prior risk factors for a trisomy 21 that were determined in an ultrasound examination, for example. For instance, the PPV of a 40 year old expectant mother for trisomy 21 is 97% due to the increased prevalence of the chromosomal disorder.

What should be considered in case of a positive result?

It is important and reassuring to know that for most women, the prenatal examinations are showing an inconspicuous test result. However, there is a chance that the result of the Harmony® Test will be conspicuous, which may lead to insecurity for you and your partner. Your responsible doctor will provide you with comprehensive information and care. If necessary, other specialists, e.g. human geneticists, should be included in the consultation. The offer of psychosocial care can also help you in such a situation in individual cases.

Limitations of the Harmony® Test

The range of analyses of the Harmony® Test is limited to the investigation of numerical disorders of the chromosomes 21, 18, 13, X and Y in the unborn child.

Many other disorders, e.g. organ malformations, can be detected by a qualified ultrasound examination in particular, but not by NIPT like the Harmony® Test. Disorders of other chromosomes - although these are rare and usually not reconcilable with the life of the child - cannot be detected with the Harmony® Test.

The detection of structural changes and partial duplications of chromosome parts are also not possible with the Harmony® Test. In particular, no hereditary diseases (such as mucoviscidosis or lactose intolerance) can presently be detected with a NIPT. Chromosome mosaics (a juxtaposition of cells with a normal chromosome set and cells with numerical chromosomal aberrations e.g. a trisomy) and chromosome translocations (parts of one chromosome merge with another chromosome) are also poorly recognized with the Harmony® Test. The restrictions mentioned here essentially apply to all NIPT procedures.

In a small percentage of cases, no test result can be obtained due to a low amount of fetal DNA or quality criteria that were not met. Cenata will not charge you for a non-evaluable Harmony® Test for trisomy 21, 18, and 13. The reason for a test failure is communicated to the responsible doctor on the report. If the Harmony® Test was not evaluable due to a low amount of fetal DNA present in the maternal blood sample, it is recommended to repeat the test a few weeks later, as the amount of fetal DNA in the maternal blood increases as pregnancy progresses. One possible cause of low levels of fetal DNA may be high maternal body weight.

In addition, it is not possible to determine the fetal gender or to carry out the analysis of the sex chromosomal disorders in a small number of samples. Causes can be both biological, i.e. as a result of an unknown vanishing twin situation (death of one fetus in the context of a twin pregnancy), chromosomal mosaicism, as well as technical reasons. In this case, a repetition of the analysis is not recommended.

Another possible cause for a failure of the Harmony® Test is an egg donation which Cenata has not been informed of. The presence of an egg donation must be stated on the Harmony® Test requisition form, as the Harmony® Test cannot generate a result if the egg donation is not known.

Procedure of the Harmony® Test

Genetic counseling

Before performing the Harmony® Test, your doctor will give you comprehensive genetic advice.

Taking blood samples

After taking blood samples, you and your doctor will fill out the test requisition form together.

Shipping samples

Your blood samples are shipped together with the test requisition form.

Performing the test

The Harmony® Test is performed, the data are analysed, and a report is prepared.

Delivery of results

Your doctor will receive the report and will adivse you of the result within the scope of another genetic counseling discussion.

When it is not possible to perform the Harmony® Prenatal Test?

The Harmony® Test cannot be performed in a multiple pregnancy with more than two fetuses. In addition, the death of a twin as part of an embryo reduction (targeted removal of one or more embryos) or a vanishing twin can lead to errors in the Harmony® Test. In such a situation, the Harmony® Test cannot be performed even if the event occurred very early in the pregnancy. The examination of sex chromosomal disorders can only be carried out in single pregnancies.

The Harmony® Test is not validated for use in pregnant women who have received organ transplants, women with active cancer, or pregnant women who have a chromosomal disorder themselves.

Consent to perform the Harmony® Prenatal Test in accordance with Art. 9 German Genetic Diagnostics Act

With my signature, I confirm that I have received extensive genetic counseling from my doctor in accordance with the German Genetic Diagnostics Act and that I have been informed about the possibilities, the significance and the limits of the procedure and understand them. I have had enough time and opportunity to address open issues. I was told that the Harmony® Test is not a diagnostic procedure and that an inconspicuous result does not completely rule out a chromosome disorder. A conspicuous result does not always mean that the fetus has an abnormality. The Harmony® Test is only one way to detect numerical chromosomal abnormalities of the unborn child, and there are other ways of screening during pregnancy that I can discuss with my doctor. I am also aware that there is a possibility of not carrying out any screening tests during my pregnancy. I am aware that the fetal gender may only be disclosed to me after the end of the 12th week of pregnancy (equivalent to week 14+0 after the first day of the last menstrual period) according to the German Genetic Diagnostics Act if I wish to know it.

Cancellation information

I can withdraw my consent to the Harmony® Test at any time without giving any reason. I have the right not to know the results of the examination, to stop the examination procedures at any time and to demand the destruction of all examination material as well as all the results of the investigation so far. In case of a cancellation, I have to bear the costs incurred until then.

Name, First Name

Place, date, time

Date of Birth

Signature

References

1. https://ghr.nlm.nih.gov/condition/down-syndrome
2. https://ghr.nlm.nih.gov/condition/trisomy-18
3. https://ghr.nlm.nih.gov/condition/trisomy-13
4. Jones, K. L., & Smith, D. W. (1997). Smith's recognizable patterns of human malformation. Philadelphia: Saunders
5. U.S. National Library of Medicine. Genetics Home Reference. Turner-Syndrome
6. U.S. National Library of Medicine. Genetics Home Reference. Klinefelter-Syndrome
7. Norton ME et al. N Engl J Med. 2015;372(17):1589-1597.
8. Stokowski R et al. Prenat Diagn. 2015 Dec;35(12):1243-6.
9. Bianchi DW, et al. N Engl J Med. 2014 Feb 27;370(9):799-808.
10. Hooks J et al. Prenat Diagn. 2014;34(5):496-499.
11. Nicolaides KH et al. Fetal Diagn Ther. 2014;35(1):1-6.
12. IFU-1290 Harmony IVD Kit Instructions for Use, Roche Diagnostics.
13. Schmid et al. Fetal Diagn Ther. 2017 Nov 8 (Epub ahead of print).
14. "Microdeletion syndrome". Genetics Home Reference. April 17, 2014.
15. Bassett et al. J Pediatr. 2011 Aug;159(2):332-9 13. McDonald-McGinn et al. Genet Med. 2001 Jan-Feb; 4. (1):23-9.
16. McDonald-McGinn, et al. (2015). 22q11.2 deletion syndrome. Nature Reviews Disease Primers.
17. NIH Genetics Home Reference https://ghr.nlm.nih.gov/condition/cystic-fibrosis#statistics
18. McDonald-McGinn et al. Genet Couns. 1999;10(1):11-24.
19. Grati et al. Prenat Diagn. 2015 Aug;35(8):801-9.
20. McDonald-McGinn et al. Genet Med. 2001 Jan-Feb;3(1):23-9.
21. Ashoor G et al. Fetal Diagn Ther. 2012;31(4):237-243.
22. Ashoor G et al. Am J Obstet Gynecol. 2012;206(4):322.e1-5.
23. Nicolaides KH et al. Am J Obstet Gynecol. 2012;207(5):374.e1--6.
24. Norton ME et al. Am J Obstet Gynecol. 2012;207(2):137.e1--8.
25. Sparks AB et al. Am J Obstet Gynecol. 2012;206(4):319.e1-9.
26. Sparks AB et al. Prenat Diagn. 2012;32(1):3-9.
27. Ashoor G et al. Ultrasound Obstet Gynecol. 2013;41(1):21-25.
28. Ashoor G et al. Ultrasound Obs Gynecol. 2013;41(1):26-32.
29. Brar H et al. J Matern Fetal Neonatal Med. 2013;26(2):143-145.
30. Fairbrother G et al. Prenat Diagn. March 2013:1-5.
31. Gil MM et al. Ultrasound Obstet Gynecol. 2013;42(1):34-40.
32. Verweij EJ et al. Prenat Diagn. 2013;33(10):996-1001.
33. Wang E et al. Prenat Diagn. 2013;33(7):662-666.
34. del Mar Gil M et al. Fetal Diagn Ther. 2014;35(3):204-211.
35. Feenstra H et al. Prenatal Diagnosis 34.2 (2014) : 195-198.
36. Juneau K et al. Fetal Diagn Ther. 2014;36(4):282-286.
37. Struble CA et al. Fetal Diagn Ther. 2014;35(3):199-203
38. Willems P et al. Facts Views Vis Obgyn. 2014;6(1):7-12.
39. Bevilacqua E et al. Ultrasound Obstet Gynecol. 2015;45(1):61-66.
40. Comas C et al. J Matern Fetal Neonatal Med. 2015 Jul;28(10):1196-201.
41. Gil MM et al. Ultrasound Obstet Gynecol. 2015;45(1):67-73.
42. Hernández-Gómez M et al. Ginecol Obstet Mex. 2015;83(5):277-288.
43. Quezada MS et al. Ultrasound Obstet Gynecol. 2015 Jan;45(1):101-5.
44. Quezada MS et al. Ultrasound Obstet Gynecol. 2015;45(1):36-41.
45. Chen A et al. Prenat Diagn. 2016 Dec;36(13):1217-1224.
46. Gil MM et al. Ultrasound Obstet Gynecol. 2016;47(1):45-52.
47. Gil MM et al. J Matern Neonatal Med. November 2016:1-7.
48. Huang S et al. Fetal Diagn Ther 2016;40(1):59-62.
49. Kagan KO et al. Arch Gynecol Obstet. 2016 Aug;294(2):219-24.
50. McLennan A et al. Aust N Z J Obstet Gynaecol. 2016;56(1):22-28.
51. Revello R et al. Ultrasound Obstet Gynecol. 2016 Jun;47(6):698-704.
52. Sarno L et al. Ultrasound Obstet Gynecol. 2016 Jun;47(6):705-11.
53. Zimmerman B, et al. Prenat Diagn. 2012 Dec;32(13):1233-41.
54. Nicolaides KH, et al. Prenat Diagn. 2013; 33(6):575-9.
55. Samango-Sprouse C, et al. Prenat Diagn. 2013 June; 33(7):643-9.
56. Dar P, et al. Am J Obstet Gynecol. 2014;211:527.e1-17.
57. Nicolaides K, et al. Fetal Diagn Ther. 2014;35(3):212-7.
58. Pergament E, et al. Obstet Gynecol. 2014 Aug;124(2 Pt 1):210-8.
59. Comas C, et al. J Matern Fetal Neonatal Med. 2015 Jul;28(10):1196-201.
60. Curnow KJ, et al. Am J Obstet Gynecol. 2015;212:79.e1-9.
61. Rapacchia G, et al. Case Rep Obstet Gynecol. 2015;2015:813104.
62. Wapner RJ, et al. Am J Obstet Gynecol. 2015 Mar;212(3):332.e1-9.
63. Gross SJ, et al. Ultrasound Obstet Gynecol. 2016 Feb;47(2):177-83.
64. Persico N, et al. Prenat Diagn. 2016 Mar;36(3):232-6.
65. Ryan A, et al. Fetal Diagn Ther. 2016;40(3):219-223.
66. Sehnert AJ, et al. Clin Chem. 2011 Jul;57(7):1042-9.
67. Bianchi DW, et al. Obstet Gynecol. 2012 May;119(5):890-901.
68. Osborne CM, et al. Prenat Diagn. 2013 Jun;33(6):609-11.
69. Futch T, et al.Prenat Diagn. 2013 Jun;33(6):569-74.
70. Srinivasan A, et al. Am J Hum Genet. 2013 Feb 7;92(2):167-76.
71. Rava RP, et al. Clin Chem. 2014 Jan;60(1):243-50.
72. Bianchi DW, et al. Obstet Gynecol. 2015 Feb;125(2):375-82.
73. Bianchi DW, et al. JAMA. 2015 Jul 14;314(2):162-9.
74. Taneja PA, et al. Prenat Diagn. 2016 Mar;36(3):237-43.
75. Grati FR et al, Prenat Diagn. 2015; 35: 801–809.
76. Stumm M, Schröer A. Gynecol. 2018, 51:24-31.
77. Lüthgens K et al. Prenat Diagn. 2020 Aug. Epub ahead of print.

vm52-V4-20220324

cenata
safe method. secure result.

harmony
PRENATAL TEST

Cenata and the Harmony® Prenatal Test –
we offer service and quality by experts

Early assurance
Applicable from gestational week 10+0 onward

Fast delivery of results
Results available in 3 working days on average

Precise and reliable
Detection rate of trisomy 21: 99.3%
False positive rate of trisomy 21: 0.04% [8]

Clinically validated with more than 148,000 pregnant women of all ages
in consistently blinded studies [7-11, 13, 21-74]

Highly qualified medical team of Cenata
Human geneticists, clinical pathologists and gynecologists can be consulted

Cenata GmbH
Paul-Ehrlich-Str. 23
72076 Tübingen, Germany

Phone: +49 7071 565 44 430
Fax: +49 7071 565 44 444
www.cenata.de/en
info@cenata.de