What does foetal exome testing mean?
The human genome consists of DNA, a molecule that contains instructions for the construction of all of the various proteins in our bodies, grouped in areas called genes. Although only a small fraction of the entirety of the DNA molecule is made up of genes, they play a major role in the inception of illnesses. Some 20.000 genes are known today, but far from all of them have a known function. A whole exome sequencing (WES) test is a genetic test that covers nearly all known disease genes and their surrounding areas, making up about 2% of the entirety of the human genome. A prenatal exome sequencing test of a foetus during pregnancy (foetal exome test) is used, in particular, to examine structural abnormalities detected in a foetal ultrasound examination.

Characteristics of the foetal exome test
Each person is an individual, and there are also a great deal of small differences in genetic makeup between different individuals. Most of these genetic differences, known as variants, are harmless in their nature, and only a fraction of them cause a known illness or predisposition to illness. Detected genetic variants are interpreted in the light of current medical knowledge. Interpreting variants may sometimes be challenging: most variants are completely harmless or benign (unrelated to any illness), for some, the significance is not known (VUS, variant of uncertain significance), and some variants are very likely or certainly pathogenic. The classification of variants may change over time as more information becomes available. A foetal exome test reports variants classified as likely or certainly pathogenic, as well as consistent with foetal findings or known to cause severe/moderate childhood illness. Variants of uncertain significance (VUS) are generally not reported. An exception is a situation where a VUS is found that appears consistent with the symptoms observed on the foetus and is considered relevant enough to report based on the assessment of a multidisciplinary team.

A foetal exome test examines a wide variety of disease genes, increasing the risk of finding a variant unrelated to the observed foetal structural abnormalities. Such findings are referred to as “other” findings. Foetal exome tests sometimes yield variants that cause severe disease in childhood, yet fail to explain findings made in the foetus during pregnancy; for example, aspartylglucosaminuria (AGU) causing developmental disability, or a severe metabolic disease, treatment for which should be started immediately after birth. The test may also sometimes indicate that the parents are carriers of a severe, hereditary childhood illness, which poses a significant risk of recurrence in any eventual future pregnancies (e.g. a situation where both parents are found to be carriers of AGU), which may have implications on family planning in the future.

The results of a foetal exome test may be added, in anonymised form, to the Clinvar variant database and may potentially be presented in scientific publications and/or congresses. The Clinvar variant database is shared by the international scientific community and allows us to better analyse and report abnormal findings in our own laboratory as well. The presentation of anonymised data in scientific publications and congresses promotes medical expertise and allows specialists to better identify rare illnesses. Personally identifiable data or identifiable

patient descriptions will never be published.

Trio tests
The aim is always to perform a foetal exome test as a trio or duo test, i.e. the sample from the foetus is examined alongside samples from both parents or one of the parents as reference samples. A trio exome test can be used to immediately detect, for example, a pattern of inheritance of variants that recessively cause inherited illness, or to determine whether a variant detected in the foetus has emerged “de novo,” i.e. not through inheritance from either parent. A de novo variant carries an increasing likelihood of being relevant to illness in the foetus. Testing the parent(s) significantly improves the chances of finding the genetic cause of foetal structural abnormalities.

Consent
Before the test, in addition to the main features of the examination, the possibility and significance of other findings (severe childhood illnesses) should be discussed with the treating physician. Trio and duo tests check the medical records of the parents in the patient information system for the purpose of referrals and the interpretation of variants.

Samples
The foetal exome test is performed on a sample of amniotic fluid or a placental biopsy and the parents' tests on a blood sample (duo or trio exome test). We always strive to provide the results of a foetal exome test within two weeks. For technical reasons caused by the laboratory, in some exceptional cases, the response time may exceed two weeks. In exceptional cases, due to technical reasons caused by the laboratory, the report for an exome test carried out very urgently may be received only after the limit of 24 weeks of pregnancy set by Valvira (the National Supervisory Authority for Welfare and Health), in which case the decision to continue or terminate the pregnancy must be made on the basis of structural abnormalities observed in imaging. DNA samples will remain stored in the laboratory for the purposes of possible future studies. After the test has been completed, the subject may, if they so wish, request in writing that their DNA sample be destroyed.

Assessment of the result
A final assessment of the link between the genetic test results and the foetal findings will be made by the physician who commissioned the test. Foetal exome testing complements foetal structural ultrasound screening, and a normal result does not certainly exclude a hereditary illness in the foetus.