



## Patient information prior to genetic laboratory analyses according to the German Gene Diagnosis Act (GenDG)

Dear patient,

You or your child has been scheduled for genetic testing. **Genetic examinations** are subject to the regulations of the German Gene Diagnosis Act (GenDG). The German Gene Diagnosis Act (GenDG) stipulates that prior to undertaking any genetic analysis, detailed medical information must be made available to the patient as well as a **written declaration of consent** must be signed.

You can revoke your consent to the analysis at any time in full or in part without stating a reason. You have the right not to be informed about test results ('right not to know'). Also, you can stop every initiated testing process at any time up to being communicated the results and request the destruction of all sample material and test results up to the time of your withdrawal. Should you have any questions regarding data protection please contact the data protection officer at Heidelberg University Hospital.<sup>1)</sup> The following text will provide you with important information about genetic laboratory analyses. Please read carefully.

### General Information

A **genetic analysis** aims at examining:

- Chromosomes, being carriers of genetic information, by means of chromosomal analysis or molecular-cytogenetic analysis
- Genetic material, i.e. DNA by means of molecular genetic analysis or. microarray analysis or
- Products of genetic material (gene product analysis) with regard to genetic traits, possibly being the underlying cause for a suspected or confirmed disease or disorder in you or your family members.

A **genetic analysis** can examine:

- In case a particular condition is suspected – specific genetic properties by means of molecular-cytogenetic or gene product analysis  
or
- Several different genetic properties at the same time using a systematic overview method (e.g. chromosomal analysis, micro array analysis or genome sequencing).

Unfortunately, no technical analysis procedure is completely free from errors. In the following, we would like to create an awareness of what type of errors could possibly occur when evaluating and interpreting medical-genetic laboratory tests.

A major potential source of error in laboratory diagnostics is that of samples being mixed up. However, we will undertake all measures to avoid such errors to occur. In the field of medical genetics, additionally, two important particularities must be kept in mind

- Often not only individuals but multiple family members are tested. Thus, for a correct interpretation of diagnostic test results, the accuracy of pedigree information is very important.
- When sampling cell material for prenatal analyses, it cannot be fully excluded that the sample may contain a mixture of fetal and maternal cells, which may lead to misleading results in subsequent analyses.

## Cytogenetic und Molecular-Cytogenetic Analyses

In cytogenetic analyses chromosomes extracted from specific body cells (generally deriving from blood, connective tissue, amniotic fluid or egg membrane (chorionic villi)) and examined by light-microscopy. **Aim of the examination** is the confirmation or exclusion of a numerically or structurally abnormal karyotype.

Please note the following:

- Occasionally, it can occur that the set of chromosomes in the examined tissue may not be representative for the whole body. This condition is referred to as "chromosomal mosaicism".
- A normal set of chromosomes in the examined tissue therefore does not fully exclude the possibility of other tissues having an abnormal chromosome set. On the other hand, an aberration in the tissue examined does not necessarily imply the set of chromosomes in other tissues being abnormal either.
- For a chromosome analysis, cells generally have to be multiplied in the laboratory beforehand. This procedure may lead to chromosomal aberrations in individual cells. Termed as 'cultural artifacts' or 'pseudomosaicisms'.
- Structural chromosomal changes can only be visualized in as far as the obtainable resolution capacity of the light microscope and the quality of the examined sample allow for. The quality of our analyses is based on the guidelines of the Professional Association of Medical Genetics (BVDH). In the case of any discrepancy based on particularities of the respective case, this will be explicitly mentioned in our diagnostic report.
- There are a number of inheritable chromosomal aberrations which are not disease-causing. These are called variants or polymorphisms or heteromorphisms and will generally not be mentioned in our results report. Given the case that such a gene variant cannot be clearly differentiated from a possibly disease-causing aberration, this will be mentioned in the diagnostic report and discussed with you.
- When performing genetic testing in multiple family members, chromosomal polymorphisms can possibly lead to a questioning of the lineage relationship. This information shall only be disclosed to you if it is essential to fulfil the examination request.
- According to the German Gene Diagnosis Act (GenDG), you will be informed of the result of the prenatal chromosome analysis by the responsible physician.
- There are cases when an individual's sex chromosomes do not match the gender-characteristics of the person. There may be biological reasons for this.

## Array Diagnostics (Molecular Karyotyping)

Molecular Karyotyping using array analysis allows for a genome-wide detection in high resolution of gains or losses of genetic material (so-called microdeletions and –duplications) within size ranges not detectable by standard chromosomal analyses. The following should be noted:

- Despite an absence of *de novo* CNVs, i.e. newly arisen smaller genetic alterations, it cannot be excluded with absolute certainty that microchanges below the detection limit may be the cause of a clinical phenotype.
- According to our present state of knowledge, familiar CNVs are generally not classified as clinically relevant variants. In individual cases and under special circumstances, it cannot be excluded, however, that familial CNVs, too, may be pathological.
- Our analysis software does currently not allow for a precise demarcation of clearly demonstrated genomic microchanges.
- This method does not allow any conclusions to be drawn about balanced chromosomal rearrangements. Neither can mosaics be excluded despite inconspicuous test results.
- **Secondary findings** may provide genetic information about the patient, which -though unrelated to the primary purpose for the testing- may result to be important as they can reveal a significant risk for developing other health conditions or predict the probability of future children developing a specific disease. When testing for 'mental retardation, developmental delay', for instance, secondary findings may indicate a genetic predisposition for a tumour disease, such as hereditary breast – or colorectal cancer. However, there is no systematical screening for genetic variants unrelated to the actual question.

## Molecular Genetic Investigations (DNA-Diagnostics)

Applying gene technological methods, molecular genetic investigations aim at identifying or ruling out genetic variants that are too small to be seen under a microscope. These analyses generally focus on individual genes (i.e. alterations of single genes). They do not aim to confirm or exclude genome-wide genetic alterations. Basically, there are two different methods to be distinguished, i.e. the so-called „direct“ and „indirect“ genetic test. Please note the following:

- Generally, so called 'direct' genetic diagnostics method is employed. In this method, the disease causing mutations prevalent in a gene can be directly confirmed or excluded. In case a mutation is detected, the validity of this result can generally be considered as high. Should an inheritable, not clinically relevant genetic variant be detected, this will generally not be mentioned or discussed in the report. Variants which are -to our current status of knowledge- of uncertain clinical significance, will be mentioned in the report and discussed with you.
- Even if there is no mutation detected in a direct gene diagnostic analysis, there can still be an underlying disease causing mutation in the gene examined or in other genes, depending on the disease, genetic disposition or the examination range

- In case a direct test does not constitute an option, an indirect genetic test may be applied. In this test, not the mutations themselves, but so called genetic „markers“ within or adjacent to the respective genes are analysed. An indirect gene test can only indicate probabilities, with their accuracy depending on the genetic relations between disease causing genes and markers. In some cases, markers may result to be totally „uninformative“, however; in these cases the test does not allow for any conclusions to be drawn.
- A (presymptomatic) molecular genetic examination of (apparently) healthy family members is possible. However, a previous consultation of a specialist in Human Genetics, or alternatively, a physician trained in genetic counselling, is obligatory.
- Occasionally, genetic family testing may reveal the biological relatedness among the family group (e.g. paternity) in fact being other than stated. We will communicate this to you only, if it is essential for the fulfillment of our investigation assignment.

### Multi Gene Panel Sequencing (MGPS)

Thanks to the introduction of Next Generation Sequencing (NGS) it has become possible to simultaneously analyse several genes in a single test. As opposed to conventional methods, where one gene at a time is analysed in a so called step by step diagnostics, NGS allows identifying a large quantity of genes and their sequence variants that have to be classified according to their clinical significance.

Please note:

- In order to ensure a correct interpretation of the diagnostic test results, a detailed description of the clinical phenotype of the patient is essential.
- Primarily we will investigate those genes, which are well-known and most frequently causative for the disease in question (primary disease-associated genes). However, the analysis can be expanded to include genes, which, for instance, have only rarely been reported in patients with the indicated disease
- Our analysis remains restricted to a specific gene segment which consequently leads to a limited clinical sensitivity.
- Similar to a single gene analysis, this method may identify variants with an uncertain clinical significance at the time of testing. Since multiple genes are being analysed simultaneously, this can occur more than once in the same test.
- Occasionally, genetic mutations are detected which -though not related to the original question- may be clinically relevant for the patient and his or her relatives (i.e. so-called additional or secondary findings).  
This information on additional findings refers to pathogenic variants in selected genes for which recognized and established therapies or early detection methods are available (according to the currently valid guidelines ACMG SF v2.0, Kalia et al., Genet. Med. 2017). In the case of minors, we only report on genetic variants already manifesting in childhood. However, there will be no systematic screening for genetic variants unrelated to the actual question. Incidental findings will not be disclosed to patients unless they have explicitly stated that they wish to be informed.

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