Benefits of genetic testing

Reveal the cause of diseases
High quality testing and good medical understanding is the most important criteria for a successful collaboration with physicians and medical specialists around the world.

We deliver sophisticated and clinical analyses including differential diagnostic and a detailed interpretation of the data.
Table of contents

Chapter 1: Introduction ............................................................................................................... 4
Chapter 2: What is a gene? / How do genes work? ................................................................. 5-7
Chapter 3: How are genes linked to a disease? ..................................................................... 8
Chapter 4: How does a mutation in a gene trigger a disease? ........................................... 9-10
Chapter 5: How do we get mutations and how do we inherit them? .................................. 11-14
Chapter 6: What is genetic testing? ......................................................................................... 15
Chapter 7: What are the uses of genetic testing? ................................................................. 16
Chapter 8: How are mutations associated with diseases identified? ............................... 17
Chapter 9: What types of diseases can be diagnosed with genetic tests? ....................... 18
Chapter 10: What is the relationship between genes and cancer? .................................... 19
Chapter 11: What are the benefits of genetic testing? ......................................................... 20
Chapter 12: What are the limitations and risks of genetic testing? ..................................... 21
Chapter 13: What is genetic counseling? ............................................................................... 22
Chapter 14: Who is a candidate for genetic testing? ........................................................... 23
Chapter 15: How can someone decide whether to have a genetic test or not? ............... 24
Chapter 16: Additional information ....................................................................................... 25
Chapter 17: The advantages of choosing genetic testing at CENTOGENE ....................... 26-27
Chapter 18: Glossary .............................................................................................................. 28-34
Chapter 1: *Introduction*

Genetic testing is a type of medical testing that identifies changes in genes. We inherit genes from our parents and we pass them to our children. Genetic tests may be used to confirm a suspected disease, or to test for an increased risk of developing a disorder that runs in a family. These tests also help us choose additional diagnostic tests (like radiological imaging), the best treatment or monitor responses to treatment. More than 2,000 genetic tests are currently in use, with more being developed all the time.

**CENTOGENE** has created this brochure in order to inform you about genetic diseases and possibilities to diagnose them by using genetic testing, as well as to inform you about the benefits and potential risks of genetic testing.

**Examples for methods that can be used for genetic testing:**

- **Molecular genetic tests (or gene tests):** Study single genes or short lengths of DNA to identify variations or mutations that may lead to a genetic disorder.
- **Chromosomal genetic tests:** Analyze all chromosomes of an individual at once.
- **Biochemical genetic tests:** Study the amount or activity level of proteins (encoded by specific genes) which may indicate a genetic disorder.

Genetic testing is voluntary. It has benefits as well as risks and limitations, thus the decision about whether to be tested or not is a personal and complex one. A geneticist or genetic counselor can help by providing information about the pros and cons of the test and by discussing the social and emotional aspects of testing.

**There are several reasons for considering a genetic test:**

- A patient or his/her child(ren) have symptoms of a disorder and you want to facilitate a diagnosis or find a biological cause responsible for the disease.
- A patient is at risk of developing this condition during lifetime.
- A genetic condition runs in the family or the patient belongs to a group or population in which there is an increased risk of a specific genetic condition and he/she want to know whether they are at risk or might pass this condition on to their child(ren).
Chapter 2: *What is a gene? / How do genes work?*

Each person has the same set of genes – more than 20,000 in total. These genes contain the information needed to make us who we are, using a kind of writing that describes how things should function. The vast majority of genetic information is identical in all humans, and the differences between people come from slight variations in the genes.

Our bodies contain more than 50 trillion cells, and nearly every type of cell has a nucleus with our genes inside. Genes are made of DNA, and DNA is ‘packaged’ in the so-called chromosomes, which we can see inside the nucleus with a microscope.

![Diagram showing the relationship between cell, chromosome, and DNA.](image)

**Fig. 1**: The genetic code of each person is inside the nucleus and organized into ‘blobs’ of DNA called chromosomes.

Humans inherit 23 chromosomes from the mother and 23 from the father – so we have 23 pairs of chromosomes (or 46 chromosomes in total). One of these pairs decides what sex we are – male or female – so these are called the sex chromosomes: X and Y.

Females inherit one X from each parent, while males get one X from the mother and one Y from the father. The other 22 pairs of chromosomes are exactly the same in males and females and are called the autosomal chromosomes.
DNA are very large molecules composed of four types of units - the deoxyribonucleotides. These four types of nucleotides, called Adenine, Thymine, Cytosine, and Guanine, are represented by the four letters in the DNA alphabet - A, T, C and G. The deoxyribonucleotides are attached to each other to form a strand.

This strand is unstable and thus, to make DNA stable, the strands pair together and twist a bit, forming the familiar spiral of a DNA helix. When strands pair together, ‘A’ always pairs with ‘T’, and ‘G’ always pairs with ‘C’.

**Fig. 2.1**: Selected parts of DNA molecules are designated as genes

**Fig. 2.2**: Nucleotides in detail: Adenine (A), Thymine (T), Cytosine (C) and Guanine (G)

**DNA alphabet**

We can picture our genome, meaning the collection of all our genes, as a library with several books that represent the chromosomes. Each book (chromosome) has a certain number of pages (genes) filled with letters (nucleotides) that are arranged in sentences (exons and introns). We can only interpret a certain part of the sentences, the exons. Other parts, the introns, cannot yet be interpreted at this time. Every page, provides instructions for the synthesis of a specific protein in our body.
Genes make proteins

**Cells use genes to make proteins** - Proteins have many different roles, they build muscles, skin, bones, and all organs, they organize cells’ shape and structure, digest nutrients, transport information, and other functions. The sum of our genetic information with the resulting proteins interact with the environment and all this together makes up all our characteristics, including color, height, personality, weight and also predisposition to diseases.

Proteins are composed of amino acids and they are made inside our cells in small ‘factories’ called ribosomes. Ribosomes receive information about the protein from genes through a messenger called RNA. This messenger RNA (or mRNA for short) is like a copy of the gene, which can travel outside the nucleus to reach the ribosome (genes can never leave the safety of the nucleus). Just like DNA, RNA is composed of nucleotides, but RNA is single stranded. It reflects most but not all of the information of the gene. This mRNA includes only exons of the genes, and not the introns.

**Fig. 3**: Molecules of messenger RNA (mRNA) are transcribed from genes (DNA molecules) and then they are transported from the nucleus to ribosomes and present the template for synthesis of a protein. Proteins are made by incorporation of amino acids, one by one, according to the codons in the mRNA molecule.

Once the mRNA reaches the ribosome, it is ‘translated’ into proteins.

The ribosome reads the mRNA, whereas the genetic ‘words’ are always made up of 3 letters.

Each group of 3 letters/nucleotides in a row is called a codon.

Each codon codes for a specific amino acid, which is added to build the protein step by step.
Chapter 3: How are genes linked to a disease?

Many diseases are called genetic diseases. They are caused by abnormalities in genes or chromosomes. Most genetic disorders are quite rare, and many conditions are present from before birth. Also, a genetic disease may or may not be a heritable disorder.

Some genetic diseases are passed down from the parents’ genes, but others are frequently or always caused by new changes to the DNA. In other instances, the same disease, e.g. some forms of cancer, may arise due to an inherited genetic condition, in new mutations or entirely due to environmental or other non genetic causes.

So far, about 6,000 known single-gene (or monogenic) disorders are known, and we test for all of them.

As their name ‘monogenic’ suggests, these diseases are caused by events in one gene, which radically changes its function, thus leading to a disorder.

Such unfavorable changes in the genetic material are called pathogenic variants and more colloquial ‘mutations’ . In contrast, many common diseases such as heart attack or diabetes are polygenic disorders and are caused by variants in several genes, frequently in combination with environmental factors.

In these cases we do not use the term ‘mutation’. The changes in genes that can lead to such common disorders may have, in another setting, advantages. Only specific combinations of genes and environment lead to the disease.

Some genetic diseases are passed on from a patient’s parents. Some develop over time.

At the moment, about 6,000 single-gene disorders are known of.

At CENTOGENE it is possible to test for all of them.
Chapter 4: *How does a mutation in a gene trigger a disease?*

If we use our ‘book and pages’ example where genes are pages, then it’s easy to imagine how ‘DNA letters’ could be accidentally switched with another letter. This kind of typo is called a variant. If this variant is unfavorable and leads to a disorder, then we may call it a mutation.

We inherit our genes from our parents and a mutation in one of these genes can be passed on from parent to child. This is why genetic diseases can run in families.

**There are many types of spelling mistakes, or many ways that a gene can be typed incorrectly in our genome books. Such errors could be:**

- The replacement of one letter or one word in the sentence - that leads to a misunderstanding of the written text (‘missense mutation’).
- The deletion or duplication of a small number of letters or words - also leading to a sentence that doesn’t make sense (‘small deletion’).
- The deletion or duplication of large sentences or even entire pages in the book - called ‘large deletion insertion mutation’.

Mistakes like these disable the gene and the protein which is produced as defect and cannot perform its functions in the cell. Sometimes, the mistake leads to the full destruction of the protein or to a defect protein that performs its functions wrongly and even has a negative effect on other functioning proteins, also leading to a disorder.
Not every change in the genetic material is a mutation. This is an aspect that is becoming more obviously now, because thousands and thousands of people are being sequenced, i.e. their genetic information is read. This leads to the identification of many millions of differences in the genetic material. Most of these are without beneficial consequences. Thus, we have to understand and define if newly detected variants will affect the function of the gene and/or the protein.

Proving that a variant is a mutation is not easy. We classify variants in order to make it easier for you and for your physician to understand and to estimate what impact a variant has. CENTOGENE follows the ACMG guidelines for classification of genetic variants, as well as additionally CentoMD®, the world’s largest mutation database. We use the below-mentioned classification scale:

<table>
<thead>
<tr>
<th>CLASS 0.1: Pathogenic</th>
<th>Variant identified according to classification system as <strong>clearly pathogenic</strong> (Class 1), but decisive information found in CentoMD® and not publicly available or due to CENTOGENE generated biochemistry/biomarker data.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLASS 0.2: Likely pathogenic</td>
<td>Variant identified according to classification system as <strong>likely pathogenic</strong> (Class 2), but decisive information found in CentoMD® and not publicly available or due to CENTOGENE generated biochemistry/biomarker data.</td>
</tr>
<tr>
<td>CLASS 1: Pathogenic</td>
<td>The variant has previously been published as <strong>pathogenic</strong> and there is no contradictory evidence available. Alternatively, there are strong internally generated biochemistry/biomarker data conclusively supporting pathogenicity.</td>
</tr>
<tr>
<td>CLASS 2: Likely pathogenic</td>
<td>The variant has not been previously published as pathogenic, however there is very strong evidence for a protein dysfunction and disease involvement. Alternatively, there are strong internally generated biochemistry/biomarker data supporting pathogenicity.</td>
</tr>
<tr>
<td>CLASS 3: VUS (variant uncertain significance)</td>
<td>Variant cannot be classified in the other classes.</td>
</tr>
<tr>
<td>CLASS 4: Likely benign</td>
<td>The variant has not been previously published as benign and frequency data of the variant strongly indicate that an involvement of the variant in the specific disease is very unlikely.</td>
</tr>
<tr>
<td>CLASS 5: Benign</td>
<td>The variant has previously been published as <strong>benign</strong> and there is no contradictory evidence available. Alternatively, there are strong internally generated biochemistry/biomarker data conclusively supporting the lack of pathogenicity.</td>
</tr>
<tr>
<td>CLASS 6: Disease-associated SNVs</td>
<td>GWAS variants which have been <strong>associated with the disease</strong> in two independent studies and variants which are only risk modifiers.</td>
</tr>
<tr>
<td>CLASS 7: Likely benign</td>
<td>Variants identified according to classification system as <strong>likely benign</strong> (Class 4), but decisive information is found in CentoMD® and not publicly available.</td>
</tr>
</tbody>
</table>

**CentoMD®** - CENTOGENE’s unique, CE-labeled mutation database with >50% of unpublished variants
Chapter 5: How do we get mutations and how do we inherit them?

Genes come in pairs, with one copy inherited from each parent. As we have seen before, genes can be spelt differently, giving rise to different versions of the same gene. These different versions are known as alleles. Depending on the functions of the gene and on the location and type of the DNA change, there are several different so-called inheritance patterns.

**Autosomal dominant inheritance**

In some genetic disorders one mutated copy of the gene is sufficient to cause the disease. It can’t be saved by the second, normal copy of the patient. These are called autosomal dominant disorders. The word ‘dominant’ means that the mutation dominates over the normal (so-called wild type) allele. Each affected person usually has one affected parent. Autosomal dominant disorders tend to occur in every generation of an affected family.

*Fig. 4*: Autosomal dominant: One parent is carrying a mutation in the gene, e.g. for Neurofibromatosis, and each of their children has a 50% risk of inheriting the disease-causing mutation from the affected parent.
**Autosomal recessive inheritance**

In some genetic disorders both copies of the gene must be mutated in order to cause the disease. These are called autosomal recessive disorders. The term ‘recessive’ means that the mutation does not show its effect if there is a wild type allele, i.e. a normal allele. Only when both gene copies carry a mutation, and no normal copy exists, the symptoms of the disorder will appear.

An affected person usually has unaffected parents who each carry a single mutated gene, and a second normal copy that keeps them healthy. In this case, the parents are referred to as ‘carriers’.

Genetic testing for the identification of their mutations is called ‘carrier testing’. Autosomal recessive disorders are typically not seen in every generation of an affected family. If parents are carriers, each child has a 25% risk of inheriting both mutated genes (one from each parent) and developing the disorder; a 25% risk of inheriting two normal genes, and a 50% risk of inheriting one normal and one mutated gene (making this person a carrier, like their parents).

---

**Fig. 5**:  **Autosomal recessive**: Two unaffected parents, each carry one copy of a mutated gene. They have one affected child and three unaffected children. Two of the unaffected children are carriers.
**X-linked linked inheritance**

X-linked recessive disorders are caused by mutations in genes on the X chromosome. In most cases, they behave like recessive disorders. Because males have only one X chromosome, a mutation in a gene on this chromosome shows its effect directly and males are more frequently affected than females, who are protected by the second, usually normal copy of the X chromosome.

The chance of passing on the disorder differs between men (Fig. 6.1) and women (Fig. 6.2). Families with an X-linked recessive disorder often have affected males, but rarely affected females, in each generation. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons (no male-to-male transmission). In these rare disorders, females are more affected than males, often because the mutation is not compatible with life if there is no second normal allele. In some rare cases, mutations on the X chromosome behave in a dominant pattern.

**Fig. 6.1**: A man with an X-linked condition has two unaffected daughters, each of whom carries one copy of the mutated gene, and two unaffected sons who do not have the mutation.

**Fig. 6.2**: An unaffected woman carries one copy of a mutated gene. She has an affected son, an unaffected daughter who carries one copy of the mutation, and two unaffected children.
Mitochondrial inheritance

This type of inheritance, also known as maternal inheritance, applies to genes in mitochondrial DNA (mtDNA). Mitochondria are little energy factories inside each cell that produce energy for the body. Mitochondria have a small amount of their own DNA (called mtDNA for short).

At fertilization only the egg cell from the mother contribute mitochondria to the future embryo, sperm cells do not. This explains why only females can pass on mitochondrial mutations to their children (Fig. 7). Disorders resulting from mutations in mitochondrial DNA can appear in every generation of a family and can affect both males and females, but fathers cannot pass these disorders on to their children.

Fig. 7.1*: Mitochondrial inheritance: A woman with a disorder caused by a mutation in mtDNA and her unaffected husband – all their children are affected.

Fig. 7.2*: A man with a condition resulting from a mutation in mitochondrial DNA and his unaffected wife – none of their children are affected.
Chapter 6: *What is genetic testing?*

A genetic test is an analysis of our DNA. This analysis can help determine if there is a mutation that can cause a disease. Genetic testing can be performed on DNA taken from blood cells, or sometimes from other body fluids or tissues. A number of different methods exist for fast and reliable testing of our DNA. The most widely known is sequencing. This means we read the text of the book letter by letter.

There are i.e. changes in the sequence, which cannot be detected by the general sequencing. Sometimes sequencing discovers changes in the DNA that are called repeat expansions. Such repeats can be compared with a multiple repetition of a single word in a text (without meaning). However, at some positions, expanding these repeats may lead to disease. One can measure the number of the repeats using a sequencing technique, which is called fragment length analysis.

Also, there are genetic tests to check if there are deletions or insertions in to the genetic material, if a paragraph, a page, or even a chapter in the book is deleted or added. There are several methods to detect such changes; MLPA analysis or qPCR analysis are the most commonly used.

Finally, DNA changes can be very large: a missing or added piece of a chromosome, an entire chromosome, or swapping of chromosome fragments (called translocation) have to be analyzed by microscopically coding at the entire chromosome.

In addition to studying chromosomes or genes, genetic testing in a broader sense may also include biochemical tests for the presence or absence of RMA, epigenetic changes (of DNA associated molecules) and biochemical tests, key proteins or of their products. As we know, proteins are made by genes, so an abnormal protein can mean that the gene is mutated.

**When does genetic testing become relevant?**

- If a **genetic disorder is suspected** and a diagnosis is sought (diagnostic testing).
- If a genetic disease **runs in the family**, some members may want to know if they’re at risk of developing this condition (predictive testing).
- If a genetic disease runs in the family, some members may want to know if they carry this disorder, and the **risk of passing** this condition to their children (carrier testing).
- Some ethnic groups have a much **higher incidence of specific genetic disorders**, so it is important that diagnostic/predictive/carrier testing is available.
Chapter 7: What are the uses of genetic testing?

Genetic tests can be used for a number of purposes - the most important ones are:

› To diagnose a disease
› To find the causative mutation (i.e. the exact change in the gene that causes this condition)
› To predict if the disease will get worse over time or not (prognosis)
› To enable physicians to manage the disease more effectively and use the best treatments available
› To search for the same genetic change in other members of the family. If people know in advance they are at risk of developing a disease, they can plan their lives with all the support they need.

Genetic tests can also be performed before a child is born: preimplantation and prenatal diagnosis. This is important in families with a known genetic disorder when couples are planning to have children. After establishing the knowledge of their risk of having an affected child through genetic carrier testing, several options are available:

› Preimplantation diagnosis (after in vitro fertilization) can be performed at a very early stage of embryo development. DNA from the embryo can be tested for certain genetic disorders. Molecular biology techniques allow to analyze this tiny amount of DNA and to distinguish between affected and unaffected embryos without destroying them. Only embryos that were tested as normal are implanted in the mother’s womb.

› Prenatal diagnosis is done at a later stage (>10-20 weeks) on samples from the fetus, e.g. amniotic fluid, chorionic villi, or fetal blood.

So genetic testing on the unborn child can be done before and during a pregnancy. Many ethical questions are still open regarding genetic testing on the unborn child. However, as genetic technologies advance, a much wider range of tests will become available for prenatal and preimplantation diagnosis.
Chapter 8: *How are mutations associated with diseases identified?*

Thanks to rapid advances in technology, new genes that are linked with diseases are being discovered at the rate of several per month. CENTOGENE is involved in several research projects to identify these genes. In a diagnostic setting, the procedure of identifying the responsible mutation in a patient starts in the physician’s office:

1. Physicians send a clinical description of their patient and request a specific genetic test - CENTOGENE provides free advice and a second opinion to clinicians about what test(s) to order to ensure the most cost-effective testing strategy for their patients.

2. If not specified by the physician, CENTOGENE selects the best testing method and uses advanced bioinformatics, specialized software, and mutation databases (including CentoMD®) to screen for disease-causing mutations.

At CENTOGENE, we offer the following types of genetic testing:

- **Hotspot Testing** – only tests for sequencing of a few common mutations
- **Full Gene Sequencing** – sequencing of the entire gene
- **Deletion/Duplication Testing** – longer sketches of missing or extra genetic material
- **Next Generation- Sequencing (NGS) panels** – sequencing of groups of genes at once
- **Whole Exome Sequencing (WES)** – sequencing of all our genes (20,000) at once
- **Whole Genome Sequencing (WGS)** – sequencing of our complete genome including genes and the non-coding sequence (20,000) at once
Chapter 9: What types of diseases can be diagnosed with genetic tests?

Virtually all disorders that have a genetic component can be predicted or identified through genetic testing. Right now we can reliably identify many of the genetic causes of the so-called monogenic disorders. These monogenic disorders are caused by one single mutation which has a big influence on specific functions. If we go back to the example of a book, it would be a typo that dramatically changes the meaning, such as forgetting a decimal point in a number and making something 1000 times more than it is in reality. These ‘catastrophic’ events influence specific functions in the body and cause symptoms accordingly.

Such mutations are nearly always inherited from one or both parents. However, sometimes a developing embryo or fetus has a genetic disorder which arises out-of-the-blue, one which is caused by a new, or de novo, mutation.

In addition to these monogenic disorders, other disorders that are called genetic complex also have a genetic component. These genetic complex disorders are often very common, such as heart attacks, diabetes, high blood pressure, etc. In such cases, a combination of genetic factors and environmental factors play a role in the disorder. Genetic testing for these disorders is still being developed, but is now available for a small portion of the cases.

A third kind of genetic changes that can be identified are the so-called somatic mutations. These mutations do not exist in all cells of the body, but only in some of the cells. The most important and well-known examples of somatic mutation that happens de novo in a cell leads to the development of cancer. Such a mutation exists only in the cancer cells and it often plays a role in its development.
Chapter 10: What is the relationship between genes and cancer?

Cancer is a disease of uncontrolled proliferation of cells in any part of the body. Cells in our bodies are under strict rules to grow and divide normally. Cancer cells break all these rules and grow out of control, forming a tumor. Cancer cells can break off from the tumor and travel to other parts of the body to start a new tumor somewhere else (this is called metastases). What causes the cell to go out of control and become cancerous in the first place?

The answer lies in the genes that control cell growth and division. Mutations in these important genes cause cancer or influence the behaviour of cancer cells.

There are two types of these mutations:

1. Germline mutations:
   We are born with these mutations (these are in our germline) and these mutations exist in all our cells. For some cancers there are genes known, which, if affected by mutations, can cause cancer.

2. Somatic mutations:
   This is the case in most cancers and these mutations occur suddenly (de novo) in one cell during our lifetime. For example mistakes can occur in our DNA when cells are dividing. Another source of mutations are certain harmful environmental agents, such as radiation or chemicals. If enough somatic mutations build up inside a cell, it can turn cancerous.

Tumor cells can be tested for somatic mutations. Every tumor has its own ‘somatic mutation’ profile and, depending on this profile, in some cases we can determine the best therapy and make a more accurate prognosis. Also, testing for these somatic mutations may help in following up on the success of a specific therapy.
Chapter 11: What are the benefits of genetic testing?

Genetic testing can be beneficial, regardless of the result:

› For some specific disorders, genetic testing may be the only way to make an accurate diagnosis.
› Once a genetic diagnosis is made, it makes further diagnostic investigations for the diagnosis unnecessary, which is good for the patient and the healthcare system.
› A definite diagnosis can be a great relief to patients and families, especially if they have been searching for the answer for a long time.
› Genetic testing can guide the physician in choosing the most suitable therapy and support for the patient.
› For some, genetic diseases good surveillance and early intervention can save the patient’s life, e.g. hereditary breast cancer caused by mutations in the BRCA1 or BRCA2 genes.
› The results of genetic testing may be useful for future family planning.
› Genetic counseling and support can be offered to families affected by a genetic disorder, helping to reduce fears, make informed decisions and plan for the future.

The accuracy of genetic test results is paramount. Major life decisions are often based on genetic test results. Therefore genetic testing should only be performed by accredited, high quality labs that regularly take part in external quality assurance schemes. Ideal patient care involves pre- and post-test genetic counseling to explain the range of options and possible outcomes, in order to obtain truly informed consent. We are entering a new era of genetic testing in which treatments will be tailored to every patient based on their ‘genetic make-up’. This is known as ‘personalized medicine’ and is part of the P4 medicine vision to:

Predict, Prevent, Personalize and encourage patients to Participate.

Fig: 8*: Medicine is now undergoing a major revolution that will transform the nature of healthcare from reactive to preventive. The changes will be catalyzed by a new systems approach to disease that will trigger the emergence of personalized medicine.

The P4 health care system includes: focus on the integrated diagnosis, treatment and prevention of diseases in individual patients.
Chapter 12: What are the limitations and risks of genetic testing?

Taking a genetic test, waiting for the results, and then receiving them may cause a range of mixed emotions such as stress, anxiety, relief, or guilt. It is important to consider the possible consequences for the person being tested, no matter if he/she receives good news or bad news.

It is important to know that:

› Specific gene tests cannot always provide a satisfactory answer.
› Despite major advances in DNA technology, identifying mutations remains a great challenge.
› Sometimes a spelling mistake is detected in a person’s DNA but there is not enough information available to tell if it is disease-causing or not. So the results are inconclusive.
› Often, a positive test is not a 100% guarantee that a person will be affected. Likewise, a negative test is not a 100% guarantee that a person will not be affected. A mutation may be present in a different gene that was not tested.
› Predictive tests often deal in probabilities, not certainties.
› Two people with exactly the same mutation in the same gene may have different outcomes. One may develop the disease while the other person remains healthy. A person’s genetic background and the environment may play a role, but the exact reasons are still largely unknown.
› Perhaps the most important limitation of gene testing is that test information often is not matched by other therapy options. For many genetic disorders, there are no effective treatments. In cancer, sometimes it is not possible to detect the disease early, even in an individual with a known predisposition.
Chapter 13: What is genetic counseling?

Because of the possible serious impact of genetic testing, people who are considering having a genetic test are strongly advised to seek genetic counseling.

Genetic counseling is the process by which patients, their parents, or family members at risk of a genetic disorder are advised by specially trained professionals who can give objective information about the consequences and nature of the disorder, the probability of developing or transmitting it, and the options available in disease management and family planning.

Genetic counseling will take into account the patient’s situation and needs and will provide him/her with information about all the options that are available, without trying to influence his/her decision in order to help make a decision regarding performing or not performing any genetic diagnosis. This complex process is followed by the diagnostic and the supportive aspects, after the results have been obtained.

In the sophisticated programs that are pioneering predictive genetic tests for cancer, genetic counseling plays a vital role. Persons considering genetic testing meet with genetic counselors both before and after the test. Before testing, the counselors try to make sure that the person is psychologically prepared to cope with the test results, and that he or she has enough balanced information to be able to formulate a truly informed consent.

If the person decides to proceed with the testing, genetic counselors help the individual and the family to adjust to the test results, and give advice to arrange whatever prevention and screening measures are appropriate.
The results of a genetic test are sensitive personal data concerning your ‘biological privacy’. They are thus considered to be confidential.
Chapter 15: *How can someone decide whether to have a genetic test or not?*

The decision to undergo genetic testing is a very personal one. It must also be voluntary. A person should agree to the test only if he/she wants to have this information and feels that he/she can handle it. No one considering a gene test should be pressured into it by relatives, health care providers, or anyone else. Every person is free to choose whether to request a genetic test or not, and also whether to be informed about the results of the test or not.

It is therefore important that a person is provided with very clear and complete information and that he/she has been given the opportunity to ask any questions or voice any concerns, to remove any shadow of doubt before taking a decision. In other words, genetic counseling should be offered, and we recommend that it should be used.

In the following are some questions listed that your patient might ask you or your genetic counselor:

About the disorder:

› What do we know about the disorder?
› Is everybody with this disorder affected by it in the same way?
› How do people live with this disorder?
› Why do I or my child have this disorder?
› Are other family members at risk of this disorder?
› Is there any treatment?
› If so, can I have access to it?
› Where can I find more information about the disorder?

About the test:

› Are there any risks in making the test?
› What will the results of the test tell me?
› How accurate will the test results be?
› Do other members of my family need to be tested?
› How long will it take before I get the test results?
› Who will have access to the test results?

Other relevant questions:

› Will the results of the test have consequences for other members of my family?
› If so, should I discuss the test with them first?
› What might be the emotional impact of the results on me, and on my family?
› Who should I tell about the test results?
› Will I get written information about what we have been discussing?
› Who can help me explain the results to my child and/or relatives if needed?
› Can these results be transmitted to other persons? If so, to whom?
› Are there any support services or patient organizations I can contact?
› What other health professionals should I get in contact with?
Chapter 16: Additional information

http://www.ncbi.nlm.nih.gov/books/NBK1116/
https://www.genetests.org/resources/genereviews.php
http://rarediseases.info.nih.gov/gard
https://www.rarediseases.org/
http://globalgenes.org/rarelist/
http://www.geneticdisordersuk.org/
http://www.mayoclinic.org/symptoms
http://www.genome.gov/10001204
http://www.geneticdiseasefoundation.org/genetic-diseases/
http://www.cancer.gov/search/results
https://ttc.nci.nih.gov/

*Image sources:

All images belong to CENTOGENE.
Chapter 17: The advantages of choosing genetic testing at CENTOGENE

- CENTOGENE offers the highest number of single gene tests and panels (multigene tests). This allows us not only to answer your specific question, but also to suggest further tests and to offer genetic tests of possible differential diagnoses.

- According to new findings and developments in the field of genetics, CENTOGENE is continually developing products and services for healthcare providers and patients.

- Our reports explain the scope of testing, offer interpretation of genetic results, give medical advice, and provide other useful items for your health and well-being. Furthermore, our clients always have the opportunity to consult with our experts without any additional costs before, during, and after testing.

- CENTOGENE offers the most attractive turnaround times for genetic testing.

- CENTOGENE requires only minimal amounts of patient samples for a genetic test; in most cases only a few spots of dried blood or saliva samples are needed. We also provide CENTOGENE’s unique filtercards (called CentoCard®) free of charge, to make it very easy to collect and send samples to our lab. The CentoCard® is a validated and stable means of collecting, sending, and storing blood samples.

- The quality of our services is guaranteed by our experienced team of experts in the fields of genetics and medicine, molecular biology, biochemistry, bioinformatics, and information technology.

- A team of highly qualified experienced scientists is responsible for the final checking, validation, and interpretation of test result data. All reports are medically validated and signed by our clinicians, who are specialists in human genetics.

- Our tests are designed with the highest standards and in accordance with the latest guidelines for the implementation of genetic tests.

- CENTOGENE uses state-of-the-art technology. All tests are carried out in our accredited laboratories, which are all internationally certified and accredited.

- CENTOGENE offers plenty of methods and technologies for genetic testing, many of those have a sensitivity and specificity close to 100%; our mutation detection rate is among the highest of all academic and non-academic institutions.

- CENTOGENE guarantees privacy and security, as all samples are encoded and documented in accordance with international regulations.

- CENTOGENE offers whole exome sequencing and whole genome sequencing (WES and WGS) combined with advanced end-to-end bioinformatic analysis, ideal for finding novel mutations and identifying atypical presentations of a disease.
Countries sending samples to CENTOGENE
A

**Acquired mutations:**
Gene changes that arise within individual cells and accumulate throughout a person’s lifetime; also called somatic mutations.

**Alleles:**
Variant forms of the same gene. Different alleles produce variations in inherited characteristics, such as eye color or blood type.

**Amino acid:**
Any of a class of 20 molecules that combine to form proteins in living things.

**Autosome:**
Any of the non-sex-determining chromosomes. Human cells have 22 pairs of autosomes.

**Autosomal dominant:**
Autosomal dominant is one of the ways that a trait or disorder can be passed down (inherited) through families. A single abnormal gene on any of the first 22 nonsex (autosomal) chromosomes from either parent can cause an autosomal disorder. In an autosomal dominant disease, one of the parents is affected with the disease and he/she also has a disease-causing mutation in one copy of the disease-related gene.

**Autosomal recessive:**
A genetic condition that appears only in individuals who have received two copies (one from each parent) of the genes with a disease-causing mutation, localized on any of the autosomal chromosomes. The gene is on one of the 22 autosomes, a non-sex chromosomes.

B

**Base pairs:**
The two complementary, nitrogen-rich molecules held together by weak chemical bonds. Two strands of DNA are held together in the shape of a double helix by the bonds between their base pairs (see ‘Chemical base’).

**Biochemistry:**
Biochemistry, biological chemistry, is a chemistry science that studies the chemical processes within living cells and organisms, at the cellular and molecular level. Biochemistry is giving us the answers about the events happening inside of the cells.
**Bioinformatics:**
Bioinformatics derives knowledge from computer analysis of biological data, popularly known as ‘in silico work’. These can consist of the information stored in the genetic code, but also experimental results from various sources, patient statistics, and scientific literature. Research in bioinformatics includes method development for storage, retrieval, and analysis of the data.

**Carrier:**
A person who carries a mutation in one copy of a gene but the other copy is normal. This is only related to recessive disorders, where both gene copies must be mutated for the disease to develop. Carriers of recessive disorders do not usually develop the disease, but they can pass the mutated gene on to their children.

**Carrier testing:**
Carrier testing is designed for healthy people who have no symptoms of disease, but who are known to be at high risk of carrying a mutation because of their family history.

**CentoMD®:**
CENTOGENE’s unique, CE-labeled mutation database with >50% of unpublished variants. CentoMD® bridges the gap between genetic variants and clinical interpretation.

**Cell:**
Small, watery, membrane-bound compartment filled with chemicals; the basic subunit of any living thing.

**Chemical base:**
An essential building block. DNA contains four complementary bases: adenine, which pairs with thymine; and cytosine, which pairs with guanine. In RNA, thymine is replaced by uracil.

**Chromosomes:**
Structures found in the nucleus of a cell which contain the genes. Chromosomes come in pairs, and a normal human cell contains 46 chromosomes, 22 pairs of autosomes and one pair of sex chromosomes.

**Cloning:**
The process of making genetically identical copies.

**Cytoplasm:**
The cellular substance outside the nucleus in which the cell’s organelles are suspended.
DNA:
The substance of heredity; a large molecule that carries the genetic information that cells need to replicate and to produce proteins.

DNA sequencing:
Determining the exact order of the base pairs, or letters, in a piece of DNA.

Enzyme:
A protein that facilitates a specific chemical reaction.

Functional gene tests:
Biochemical assays for a specific protein, which indicates that a specific gene is not merely present but also active.

Gene:
A unit of inheritance; a working subunit of DNA. Each of the body’s 20,000 to 25,000 genes contains the code for a specific product, typically, a protein such as an enzyme.

Gene deletion:
The total loss or absence of a gene.

Gene expression:
The process by which a gene’s coded information is translated into the structures present and operating in the cell.

Gene mapping:
Determining the relative positions of genes on a chromosome and the distance between them.

Gene testing:
Examining a sample of blood or other body fluid or tissue for biochemical, chromosomal, or genetic markers that indicate the presence or absence of a genetic disease.
**Gene therapy:**
Treating disease by replacing, manipulating, or supplementing nonfunctional genes.

**Genetics:**
The scientific study of heredity: how particular qualities or traits are transmitted from parents to offspring.

**Genome:**
All the genetic material in the chromosomes of a particular organism.

**Genotype:**
The actual genes carried by an individual (as distinct from the phenotype) from the physical characteristics.

**Germ cells:**
The reproductive cells of the body, either egg or sperm cells.

**Germline mutation:**
See ‘Hereditary mutation’

**Hereditary mutation:**
A gene change in the body’s reproductive cells (egg or sperm) that becomes incorporated in the DNA of every cell in the body; also called germline mutation (see ‘Acquired mutations’).

**Human genome:**
The full collection of genes needed to produce a human being.

**Human Genome Project:**
An international research effort aimed at identifying and ordering every base in the human genome.

**Imprinting:**
A biochemical phenomenon that determines, for certain genes, which one of the pair of alleles, the mother’s or the father’s, will be active in that individual.
**M**

**Mutation:**
A change in the number, arrangement, or molecular sequence of a gene.

**MLPA:**
Multiplex ligation-dependent probe amplification is a variation of the multiplex polymerase chain reaction that permits multiple targets to be amplified with only a single primer pair.

**N**

**Newborn screening:**
Examining blood samples from a newborn infant to detect disease-related abnormalities or deficiencies in gene products.

**Nucleotide:**
A sub-unit of DNA or RNA, consisting of one chemical base plus a phosphate molecule and a sugar molecule.

**Nucleus:**
The cell structure that houses the chromosomes.

**O**

**Oncogenes:**
Genes that normally play a role in the growth of cells but, when overexpressed or mutated, can cause cancer.

**P**

**Penetrence:**
The likelihood that a given gene mutation will actually result in disease. Often it is 100%, but not always.

**Predictive gene tests:**
Tests to identify gene abnormalities that may make a person susceptible to certain diseases or disorders.

**Prenatal diagnosis:**
Examining fetal cells taken from the amniotic fluid, the primitive placenta (chorion), or the umbilical cord for biochemical, chromosomal, or gene alterations.
Protein:  
A large, complex molecule composed of amino acids. The sequence of the amino acids and thus the function of the protein is determined by the sequence of the base pairs in the gene that encodes it. Proteins are essential to the structure, function, and regulation of the body. Examples are hormones, enzymes, and antibodies.

QPCR:  
Real-time PCR, also called quantitative PCR or qPCR, can provide a simple and elegant method for determining the amount of a target sequence or gene that is present in a sample.

Reproductive cells:  
Egg and sperm cells. Each mature reproductive cell carries a single set of 23 chromosomes.

RNA:  
A chemical similar to DNA. The several classes of RNA molecules play important roles in protein synthesis and other cell activities.

Sensitivity:  
Refers to the ability of a particular test method to correctly identify the presence of a mutation (detected true positives). The higher the test’s sensitivity, the better the likelihood that it will identify a mutation. In most medical tests, there is a risk of identifying a normal sequence as mutated ≈ false positives.

Sex chromosomes:  
The chromosomes that determine the sex of an organism. Human females have two X chromosomes; males have one X and one Y chromosome.

Somatic cells:  
All body cells except the reproductive cells.
Specificity:
Refers to a test’s ability to correctly identify normal gene sequences (avoids false positives). The higher the specificity, the lower the likelihood that a normal sequence will be diagnosed as mutated. It is important to have high sensitivity coupled with high specificity to lower the risk of detecting false positives.

Transcription:
The process of copying information from DNA into messenger RNA (mRNA). The mRNA then carries this information to the ribosomes, where it serves as the blueprint for the manufacture of a specific protein.

Translation:
The process of reading mRNA, to make a protein, one amino acid at a time. This process takes place in the cytoplasm, on structures called ribosomes.

X chromosome:
A sex chromosome; normal females carry two X chromosomes.

Y chromosome:
A sex chromosome; normal males carry one Y and one X chromosome.
To choose the most suitable therapy and support for the patient - this is what genetic testing is all about.
Please visit our website for more information:

www.centogene.com

Contact details:

CENTOGENE AG
Doreen Niemann
Senior Director Strategic Communication
Schillingallee 68
18057 Rostock
Germany

Email: dmqc@centogene.com
Phone: +49 (0)381 203 652 - 222
Fax: +49 (0)381 203 652 - 119

CLIA #99D2049715