Intervening in our DNA

how far can you go?

npv
zorg voor het leven

"Your eyes saw
my unformed body"
(Psalm 139:16, Berean Study Bible)

Introduction

Dear reader,

Good health is important to many people. At the same time, we are vulnerable. We can get sick or become disabled. When that happens, it is nice to know you can get proper treatment. Anyone with a hereditary disease knows that treatment cannot be taken for granted. Hereditary diseases are related to our DNA, and DNA cannot be changed just like that. In this brochure you will be able to read about developments in the treatment of hereditary diseases, and all the positive - and less positive - consequences this has.

From parent to child

Hereditary diseases can be passed on from parent to child. Here we immediately have the problem of hereditary diseases. If (one of the) parents has such a disease, their child can also get it. You don't have to be ill to pass on a hereditary disease. Some parents are healthy, but "carry" a mutation,* which is a change (often harmful) in DNA. If the parents who are carriers of such a mutation are healthy, their child may still develop the disease.

> ''Gene therapy is a new development in medicine with - seemingly - great potential. But it also carries major risks and poses serious ethical questions''

Some hereditary diseases can be treated. For example, through a special diet or by taking medication. But for many such diseases, no good treatment has yet been developed. That's why a great deal of research is being done to develop new treatments. One of those new treatments is gene therapy. Gene therapy restores a harmful change (a mutation) in the DNA. The DNA is therefore adjusted so that the disease disappears.

Adjustment of DNA

DNA can be modified in cells of the body. In theory, it is also possible to modify DNA in the human embryo. We call this germline gene therapy or germline gene editing. If the editing of the DNA in the embryo succeeds, then this person will be rid of the disease for the rest of his life. And not only that: It is possible that (grand)children will not get the hereditary disease either.

Possibilities and risks

Gene therapy is a new development in medicine with - seemingly - great potential. But it also carries major risks and poses serious ethical questions. In this brochure we tell of these developments. We explain what gene therapy and germline gene therapy is. You can read about the possibilities these therapies offer. But also about the difficult questions and risks with which it faces us. Changing people's DNA is drastic. Today's discussion may one day become actual treatment. At that time you will have to make your own decision in your doctor's office. Perhaps this hits even closer to home for you, for example because your child has a hereditary disorder or because you yourself have a mutation in your DNA.

We cordially invite you to discover with us what (germline) gene therapy exactly is and what it means for you and for us. We hope that when the time comes, this brochure will help you to make informed and responsible choices.

January 2021,

Henk Jochemsen
Elise van Hoek

* The meaning of words in pink can be found on page 25.

Lotte's heel prick
Like almost all newborn children, Lotte received a neonatal heel prick eight days after her birth. "No news is good news," they added. But two days later, the doctor was on the doorstep. The first analysis showed that Lotte had a rare condition called tyrosinemia type 1. A follow-up investigation revealed that Lotte lacked an enzyme important for the metabolism in her body. The fact that this protein was not in her cells was due to a mutation, a change, in her DNA. By adhering to a special diet - which is quite intense - and taking medication, Lotte is still able to grow up in health. Fortunately, the heel prick provided a quick early warning!

Source, in Dutch: https://www.nemokennislink.nl/publicaties/dankzij-de-hielprik-is-lotte-niet-ziek-al-heeft-ze-wel-een-ziekte/

What is heredity and how does it work?

Genetic research for everyone

Lotte's example (see box) shows that almost all parents in the Netherlands have to deal with genetic research. The blood taken in the heel prick is tested for more than twenty congenital disorders. Hereditary disorders as well. By treating such a condition immediately after birth, the consequences of such a condition are where possible reduced.

Let's start with the question of what exactly heredity is. How do parents' traits end up in their children?

Building blocks of people

The human body is made up of trillions of cells (see figure 1). Every cell has a nucleus. The nucleus contains chromosomes, usually in 23 pairs. Each pair has one chromosome from the mother and one from the father. A chromosome consists of a spiral-shaped molecule: DNA. This DNA contains all of a person's hereditary information. A piece of DNA that provides information about a property is called a gene.

For example, there are genes for eye color and for metabolism.

Research shows that DNA consists of a very long, spiral-shaped chain of small building blocks called "nucleotides". There are four types of nucleotides. The sequence of these nucleotides determines the hereditary information of a human. We can compare this with written text. The order of the letters together make a word. And several words together make up a sentence. This creates "sentences" (genes) for the color and shape of the hair, for eye color, and so on. All properties of a human have to do with the information in these pieces of DNA. Figure 1 below shows how this works.

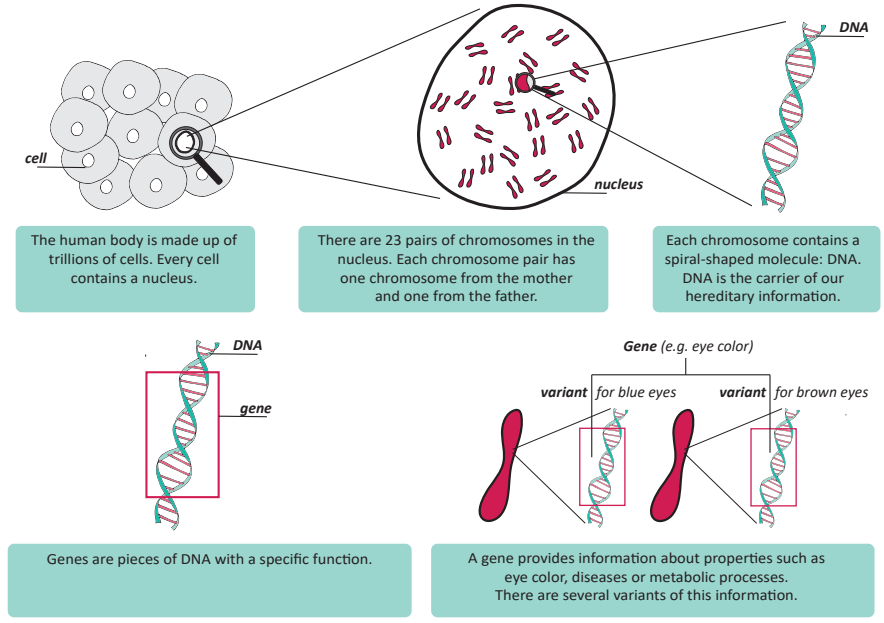

Figure 1 What is DNA and where can you find it in the body?

A unique combination

Children resemble their parents and at the same time are unique individuals. Let us tell you how this is so. We have already read that every normal human body cell (usually) has 23 pairs = 46 chromosomes. When the body makes egg cells or sperm cells, the 23 pairs are divided among the egg cells or sperm cells. Each egg cell or sperm cell therefore contains 23 chromosomes.

During fertilization, the egg cell and sperm cell fuse together. They then each bring their 23 chromosomes together. The fertilized egg cell therefore contains 46 chromosomes. Each pair is now complete. This combination of the male and female chromosomes - the DNA - determines the child's hereditary characteristics.

After fertilization, the embryo divides into two cells, which then divide again. This creates a lot of cells and the embryo grows into a baby. Because the DNA in all those cells comes from the parents, the child looks like the parents. But the combination of the chromosomes is unique, which is why every child is a unique person (see figure 2).

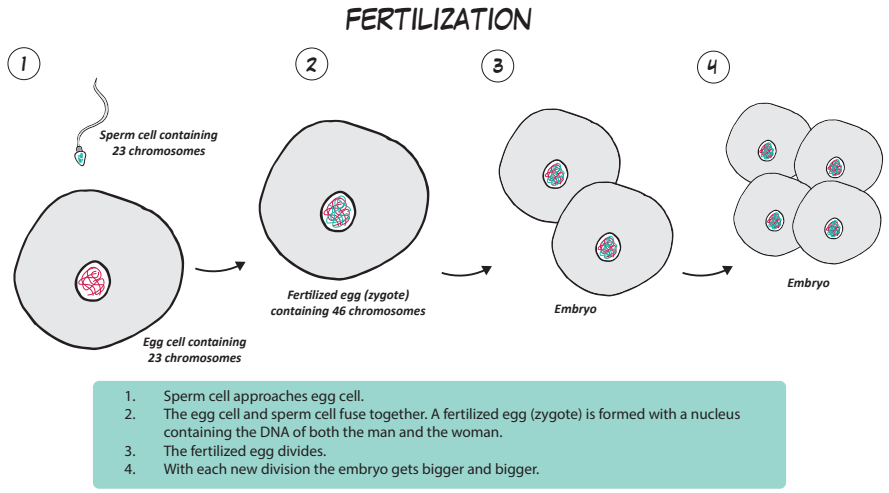

Figure 2 During fertilization, an egg cell and a sperm cell come together. Together they form a new embryo, the start of a new human life.

Getting a hereditary disease

The DNA that a child receives from parents influences all of its properties. This also applies with regard to diseases and disorders.

If the parents pass on a harmful abnormality in the DNA to the child, we speak of a hereditary disease or disorder. Sometimes one or a few letters (nucleotides) are missing, or a letter is in the wrong place, so that the message is no longer correct. We call that a "mutation" of the gene. Examples of diseases that can develop as a result of this are cystic fibrosis and Duchenne's disease.

Sometimes a disease is not hereditary, but still has to do with the DNA. The best-known example is Down's syndrome. People with this condition have three times chromosome 21 in their DNA, instead of two times. We call that "trisomy 21".

Facts and figures regarding hereditary disorders

- Most children are born healthy. The chance that a child will be born with a disease or disorder is small.
- A genetic cause has been discovered for more and more disorders, allowing them to be diagnosed soon after birth.
- More than 6,000 different hereditary diseases are now known.[1] Many of these diseases are caused by a mutation in one gene. We call this a **monogenic disorder**.
- Although these diseases are rare, it is estimated that about 1 million (almost one in sixteen) Dutch people have a hereditary disorder. About 75 percent of these diseases manifest themselves in childhood.
- Most hereditary diseases and disorders cannot (yet) be treated.
- The genetic cause of approximately 10,000 hereditary disorders, including cancers, is known.[2] This may be a first step towards treatment, including some form of gene therapy.
- It has been calculated that about twenty percent of the healthcare budget in the Netherlands is spent on the treatment of complaints or characteristics associated with hereditary diseases.

1. See https://download2.eurordis.org/pressreleases/PrevalencePaper_JointStatement_170919_Final.pdf
2. https://www.ncbi.nlm.nih.gov/gtr/

Not every mistake in the DNA has serious consequences. That depends on all kinds of factors, such as the environment and other information in the DNA. With Lotte's disease (see box on page 4), the error in the DNA does not have to have serious consequences. If this disease is discovered soon after birth, a diet can help Lotte to live with it. The extent to which the disease manifests itself can therefore differ per person.

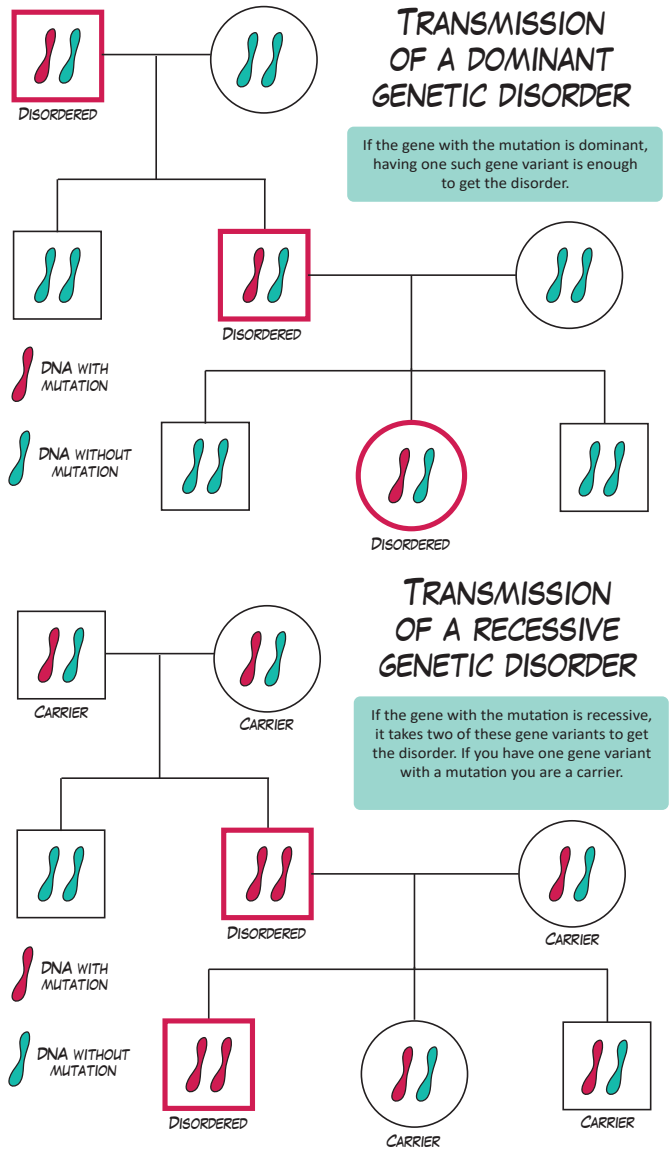

Figure 3 Parents can pass on a hereditary disease to their children and grandchildren. A disease or abnormality is dominant genetic if one abnormal gene (from a pair of genes) is sufficient to cause the disease. Often one of the parents has the disease. A disease or abnormality is recessive genetic if this disease or abnormality only manifests itself when both genes of a certain gene pair are abnormal.

Gene therapy: a new way of treating

More and more treatments are available for people with a hereditary condition (see box with facts and figures on page 7). Doctors often try to reduce or prevent the consequences of a mutation in the DNA by means of lifestyle, medicines and therapies. Now there is another way to treat hereditary diseases: gene therapy. With gene therapy you not only treat the complaints or characteristics that accompany the disease, but you remove the cause of the disease - the mutation.

CRISPR-Cas

Since 2012, it has been technically possible to change human DNA with special biotechnological tools - CRISPR-Cas (see figure 4). CRISPR-Cas consists of two parts, a protein (Cas) that can cut DNA, and a guide molecule (very similar to DNA) that indicates to the protein where to cut. You could compare CRISPR-Cas with the cut and paste function on the computer. The DNA with the mutation is cut and replaced with DNA without mutation, so that the "word" is correct again.

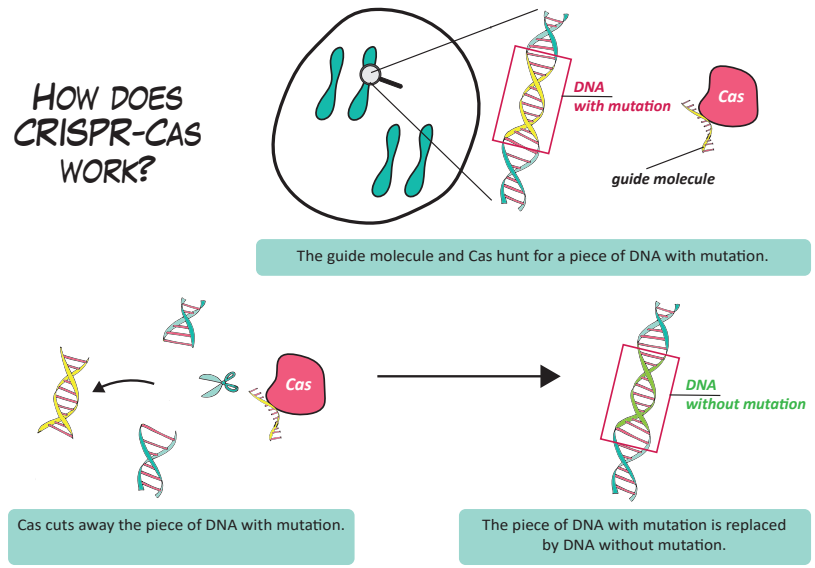

Figure 4 Correction of a mutation by CRISPR-Cas

Two approaches to gene therapy

There are two ways in which gene therapy can be used: gene therapy in the *body cells* of children and adults, and gene therapy in the germline, which contains the sex cells of parents or the embryo. Let us explain both forms of gene therapy.

Gene therapy on body cells

Gene therapy on cells in the body is also called somatic gene therapy. This form of gene therapy restores the mutation in the cells of the patient. This happens in the cells in which the mutation causes the most problems. For example, if a patient has cystic fibrosis, the mutation in the lung cells is restored.

Years of research have been conducted into this form of gene therapy. Nevertheless, restoring body cells with a mutation has turned out to be more difficult than was hoped and expected. Even so, developments have been rapid in recent years (see "Treatment with a price tag" in the box below). For example, gene therapy has also been found to help treat non-hereditary diseases such as AIDS and forms of cancer.

Depending on the research, gene therapy can be used for more than just the cure and treatment of hereditary diseases. It may also become possible to produce desirable traits in humans. A certain hair color, or

Treatment with a price tag

In May 2019, the world's most expensive drug, Zolgensma, was approved for sale on the US healthcare market. Zolgensma is a gene therapy for spinal muscular atrophy (SMA), a muscle disease that often causes children to live less than two years. The gene therapy transfers the genetic material of the missing SMN protein into the nerve cells. This enables the cells to begin producing their own protein. Although it is a one-time treatment, it comes with a price tag of €2 million.

See https://www.biomaatschappij.nl/gentherapie-belofte/

extra muscle development, for example. This is not yet being done; whether it ever will happen is uncertain, but in our opinion it is not inconceivable. For this reason we will return to this issue later in the brochure to discover how we can deal with it.

Germline gene therapy

The second form of gene therapy - *germline gene therapy* - ensures that a mutation that runs in the family cannot be passed on to the next generation. This form of gene therapy is not yet sufficiently developed to be put to use. But if the time ever comes, people with a hereditary disease who want to have children can opt for germline gene therapy. This works as follows. The embryo is formed in the laboratory via in-vitro fertilization (IVF). The mutation is changed in this embryo so that it grows into a mature person without hereditary disease. The disease is therefore kept from being passed on to subsequent generations.

Figure 4 shows how a mutation in an egg cell, sperm cell or in a single-celled embryo could be treated. We say "could be" consciously, because this treatment is currently still in the research phase.

'Germline gene therapy is a new step in medicine'

In germline gene therapy, the mutation is changed in the single-celled embryo, the first phase of human life. This is understandable from a technical point of view, because the embryo now consists of only a few cells and is very manageable. But at the same time, the risk of errors is high in this phase. And an error can have major consequences in a growing embryo, such as miscarriage or serious congenital health problems.

Growing concerns

Germline gene therapy is a new step in medicine. It is now illegal worldwide to use the therapy in humans. There are still all kinds of questions and opinions: Is the technology safe? When things go wrong - and where people are at work, mistakes are made - what does that mean for future generations? More research is needed to answer these questions. Research which requires human embryos. But is that justifiable? And if the research succeeds, how far will we go in "adapting" embryos to our wishes? You understand: expectations are high, but there are also feelings of unease and resistance. In the next section, then, we will look for an answer to the question of what is right and good, and what is not..

May we intervene in man's DNA?

The DNA we get from our parents is closely linked to who we are. And is it not true that our hereditary material is given to us personally by God, our Creator? Can we make changes to that? These are important questions that we want to consider carefully.

Our identity

From the Creator we get our body as a whole, not just our DNA. Sometimes people are born with illnesses, disabilities or malformations. As difficult at times as that may be, God also controls those things. That does not mean that we can see God as the cause of evil, such as disease. Jesus himself healed people with all kinds of ailments and deformities. He did so out of compassion, and to show that diseases are neither part of God's creation nor His future.

Although we get our DNA from our Creator, we are not the same as our DNA. Our identity - who we are - is so much more than that. Fortunately, in some cases it is possible to treat a hereditary disease in a safe manner through this DNA in our cells. If this is indeed done safely, there is no reason in principle to stop the treatment. Many cancer treatments have been applying DNA interventions for some time now, in order to better combat the disease. So why is it important to be careful? We will explain that next.

Safety as precondition

With a new medical treatment, safety is very important. This also applies to *gene therapy*. For some diseases, *gene therapy on body cells* is a safe treatment. This is different with germline gene therapy. Scientists

are still debating the safety of this technique. CRISPR-Cas (see p. 10) appears to be a promising way to use germline gene therapy in the future. But first it must be clear whether this is safe enough to be used. The lack of clarity is why professional organizations of geneticists and embryologists think it is (far) too early to treat patients with germline gene therapy.

If it is possible to make germline gene therapy safe - we are not sure whether this will be possible - then the therapy initially will only be for serious hereditary disorders in a single specific gene. For disorders involving multiple genes (and environmental influences), the treatment is too difficult and dangerous to perform.

'We believe that the human embryo is a unique being from the very beginning'

Human embryos

To find out whether germline gene therapy is safe to use as a treatment, human embryos are needed. These embryos are used for further research into the therapy. Researchers would like to start culturing embryos for this research. This is currently prohibited. Some researchers and practitioners would like this ban to be lifted.

Researchers currently use "residual embryos" for their research. These are embryos left over from fertility treatments, such as IVF. The use of residual embryos, but also the culture of embryos, is a major moral problem in our view. We believe that the human embryo is a unique being from the very beginning. In fact, the fertilized egg is the only cell that has all the properties to grow into new, unique human life. And this is true from the moment of fertilization - the fusion of the 46 chromosomes.

Animated being

Besides the body, people also have a spiritual side, which from the very beginning has been closely linked to the body. In more Biblical language we say: from the beginning, an embryo is an animated human being. For Christians - as well as for Jews and Muslims - God is the Creator of life, and of every human being in particular. He ensures that every new person grows in body and spirit (Psalm 139). He does that in the way of nature, a way in which things can go wrong, such as a mutation in the genes. They are not part of God's original purpose. Man himself is. People with disorders of any kind are created in His image, which is why we must protect them.

The embryos used for research have no chance to develop into full-grown babies. They are not seen as human life, but as research material. If no other ways are found to develop germline gene therapy, we see this as an insurmountable problem.

The He Jiankui case

In November 2018, Chinese physician/researcher He Jiankui announced that he had used germline gene therapy with twin sisters Lulu and Nana. He changed a gene in the embryos that prevented the babies from contracting HIV. To do this, he used the CRISPR-Cas technique. In doing so, He switched off the piece of DNA that ensures the production of a protein that gives the HIV virus access to a cell. If that protein no longer works, the virus can no longer enter the cell.
The report caused a lot of commotion because it was not yet known whether the technology was safe and would work properly. So at the time it was an ethically unacceptable intervention. It later turned out that technical errors had also been made. He Jiankui was sentenced to three years in prison and a hefty fine.

Opinions regarding embryos

Residual embryos are left over after fertility treatments. Parents made egg and sperm cells available for pregnancy. Embryos that are "left over" and not placed in the uterus are sometimes used for research. We call this research with residual embryos. With cultured embryos we go a step further. We make these especially for research. The purpose of these embryos is not pregnancy, but use as test material.

Research institutes

Schuttelaar & Partners and the Rathenau Institute have independently researched the question of how people think about human embryos. They asked questions about scientific research with *cultured embryos* and embryos that remain after IVF, so-called *residual embryos*. Briefly summarized, Schuttelaar discovered that 75 percent of the population agrees with research using residual embryos, but only under certain conditions. Rathenau's research indicated that 39 percent of respondents agree subject to conditions when it comes to residual embryos, while 26 percent tend to agree (total 65 percent). Research with *cultured embryos* is acceptable to 64 percent of the population under certain conditions (Schuttelaar). At Rathenau, 23 percent agree subject to conditions, while 26 percent tend to agree (total 49 percent). For the political discussion on this topic, it is important to note that part of the population sees a moral difference between research with residual embryos and with cultured embryos.

Christian organizations

In addition to the above research, the Christian organizations NPV, Reformatorisch Dagblad and the Prof. Lindeboom Institute have conducted research both among their supporters and the Dutch population. The question was which goals were considered important enough for the use of embryos for research. In this study, no distinction was made between residual and cultured embryos. The investigation revealed that among the Dutch population in general, between 30 and 55 percent find all kinds of suggested reasons for research acceptable.

This would include the treatment of hereditary diseases in adults, the development of new techniques, the editing of the DNA of embryos, the prevention of hereditary diseases, the development of stem cell research and research into infertility. Among the aforementioned supporters, only a small minority (max. 13 percent) considered these goals important enough for embryo research. In the 18-30 age group, acceptance of embryo research is relatively high for most purposes, especially for research on infertility.

Consequences for future generations

Intervening in the DNA of an embryo has consequences not only for the here and now but also for future generations. Just as hereditary diseases can be passed on, adaptations in the DNA are also passed on to children and grandchildren. That is far- reaching. These people are not yet alive and cannot give their consent. It is true that parents often make important decisions for their children. And many children would be happy not to get the hereditary disease! But when is a disease serious enough to intervene?

Positive effects

We know that some mutations in the genes can have not only detrimental but also positive consequences. A well-known example is the hereditary disease *sickle cell anemia*. People with that disease are less likely to get malaria than healthy people. With several hereditary diseases, a mutation can have negative and positive consequences. Increased use of *germline gene therapy* means that parents and doctors are now deciding on the hereditary traits of generations to come. And that while we do not know which properties will be needed in the future. Are we not deciding too much about human life (of the future) in germline gene therapy?
Especially when we realize that the question is whether we will ever be able to use the technology safely.

The hereditary material of each person, and the way in which this uniquely shapes people, turns out to be more complicated than previously thought. And it is precisely the embryo, in which a great deal of genetic information has to be used at the just right time, that is very vulnerable. It is nice when we strive to do good and avoid suffering. But virtues like modesty and prudence are also essential here!

Medical-ethical principles
Often mentioned medical-ethical principles are: do good, do no harm, autonomy (which means, above all, freedom of the patient to decide whether or not to undergo treatment), and fairness in the distribution of resources. How someone feels about these kinds of things depends on a person's philosophy or beliefs.

Dealing with brokenness and suffering

When we talk about treating illness, we should also talk about the way we deal with disorders and illnesses. Research has shown that children have a greater chance of developing (psychologically) positively if their parents accept them unconditionally. These days, unfortunately, perfection is often the standard. As a result, it can just happen that we no longer see life as it is given to us, and no longer recognize the vulnerability of humans. The well-known writer C.S. Lewis called suffering "God's megaphone." Because in suffering, for example due to a hereditary disease, God announces with a booming voice that life outside of Him is not what it should be. And not only for the sick, but for everyone.

Being vulnerable

The other way around also happens. Sometimes the way a person deals with a disease or disorder shows something of God's work in people's lives. We are consciously being cautious about the way in which we speak of this. Suffering can be so intense that people can no longer bear it. Denying or ignoring the vulnerability of people means that we are less able to sympathize and empathize with others.
Perhaps we can even say that it is only after we have become vulnerable ourselves that we can truly empathize with other vulnerable people. In fact, if we don't see our own vulnerability, we may start to see hurt people - the sick, people with disabilities - as a less successful form of humanity. Just think of the reactions people have when a child with a disability is born: "That is no longer necessary - you are burdening society with expenses." We do not want such a society!

Enhancement medicine

It is important to think about how we want to deal with vulnerability and suffering. If germline gene therapy can be developed without the use of human embryos, we still have not arrived. Germline gene therapy can also be used to promote or even impart certain desirable properties in a healthy person. We believe that this is contrary to the dignity of man, who is created in God's image.

Anyone who tries to improve a person actually is saying that normal, healthy physical existence is not good enough. The body is then used to make life "above normal." We believe that the body is not an instrument to be improved. If enhancement medicine goes beyond treating sickness and suffering, it is a human anticipation of the Kingdom of God. A Kingdom in which the citizens will have a "glorified" body (1 Corinthians 15: 35-49). And it detracts from the God-given dignity of man.

'Anyone who tries to improve a person actually is saying that normal, healthy physical existence is not good enough'

No longer of equal value

Enhancement medicine also causes the relationships between people to change. One person can become the design or project of another. This is a development that we are already seeing in assisted reproductive technologies, combined with genetic research. For example in foreign clinics where parents can choose the sex of their child themselves. In such cases, the relationship between parent and child changes from giver-receiver to maker-made. As a result, the crucial equality between parent and child disappears. What is made is not equivalent to its maker. In short: if germline gene therapy becomes possible, we find that acceptable only for the treatment of serious conditions.

Finally, enhancement medicine is contrary to medicine's nature. For a long time, medicine has sought to prevent and cure disease and to remedy or alleviate suffering. Medicine is about recovery, not improvement. This certainly applies to the medical care that we pay for through insurance. When medicine is used to make someone "different" or "better," the role of medicine in our society has changed. We already see this happening, for example, in cosmetic surgery.

If germline gene therapy becomes possible, there is a risk that all kinds of boundaries will shift. Because for which condition will the procedure be allowed to be used? In our society we find health, beauty, being energetic, being able to produce and consume to be very important. People are willing to go further and further in order to live the desired life.

For further consideration

Gene therapy on body cells

Instead of *germline gene therapy*, it is possible in some cases to use *gene therapy on body cells*. Its development is much further along than that of germline gene therapy.
The advantage is that only one patient is at risk, rather than all subsequent generations. The disadvantage is that every patient must be treated with the therapy, sometimes very soon after birth. It is also true that there are many hereditary conditions for which this form of gene therapy at best only helps a little. Furthermore, the question is whether this form can always be used in time, perhaps even before birth, to prevent damage to a child.

SHEEFs

As mentioned, the use of embryos for germline gene therapy research is a major problem. Over the past five to six years, it has been possible to form cells in the laboratory that closely resemble embryos. They are called Synthetic Human Entities with Embryo-like Features (SHEEFs). The SHEEFs look a lot like embryos, but - it now seems - cannot develop further. If this is indeed so, then there is no early human life. In which case, these SHEEFs can be used for research into germline gene therapy. This requires further research into SHEEFs, namely whether or not they should be seen as embryos, and when exactly they can be used. Further scientific investigation and ethical reflection is needed to answer the question as to whether we can view SHEEFs as an acceptable alternative.

Germline gene therapy via a detour (figure 5)

To use germline gene therapy in patients, it must be safe. If a mutation has been edited, it is tested to see whether the change went well. The embryos used for research into safety do not survive. We said above that we find this unacceptable. And not only we, for across the broader society there are also objections (see box: Opinions regarding embryos, pages 16-17). Researchers are therefore thinking about other ways to develop germline gene therapy. A way that requires fewer embryos. What does that way look like? It turns out to be possible to grow cells from mice in the laboratory, in culture, into germ cells. This is called In Vitro Gametogenesis (IVG). It is special: "normal" cells that make egg

cells or sperm cells in a dish. If this also works in humans, it would be possible to grow egg cells and sperm cells in the laboratory from people from whom normal body cells have been taken. Once again, this way raises many ethical questions, but for now we are looking at the question of whether it will be possible to make germline gene therapy possible in this way.

'Medicine is about recovery, not improvement'

In short, this would work in the following way. A patient has a mutation which makes, or could make, him become seriously ill. This patient would like to have children, but without the mutation. Normal body cells are taken from the patient and put in culture. In those cells the mutation is changed. The procedure can be easily monitored in them. The corrected cells are allowed to grow into sperm cells or egg cells depending on whether the patient is a man or a woman. Using the corrected sex cells, an embryo is made via IVF, which is then inserted into the woman's uterus.

The question remains whether the sex cells that grow in the dish can ensure proper fertilization from which a healthy embryo can grow. Researchers will want to know for sure before using embryos in this way for IVF treatment. So many questions remain. For an ethical discussion of some of those questions, we refer to the book *Geboren, niet gemaakt* (see the bibliography at the back). We cannot go into that now. We mainly mention the development here because it might take place in the coming years.

IVF as basic technique

It is clear from the above examples that germline gene therapy can be performed only if the pregnancy is achieved through IVF (test tube fertilization). This brings up all kinds of ethical questions. Ideas about IVF vary among orthodox Christians. Some find IVF acceptable under certain conditions, such as if no residual embryos are frozen. Others reject IVF. We will not go any further into this now, but we would like to mention it.

Gene therapy and germline gene therapy seem to be good treatments for some hereditary diseases. You have read about that in this brochure. There are still many questions surrounding germline gene therapy. As long as we do not have good answers, we believe that germline gene therapy should remain prohibited.

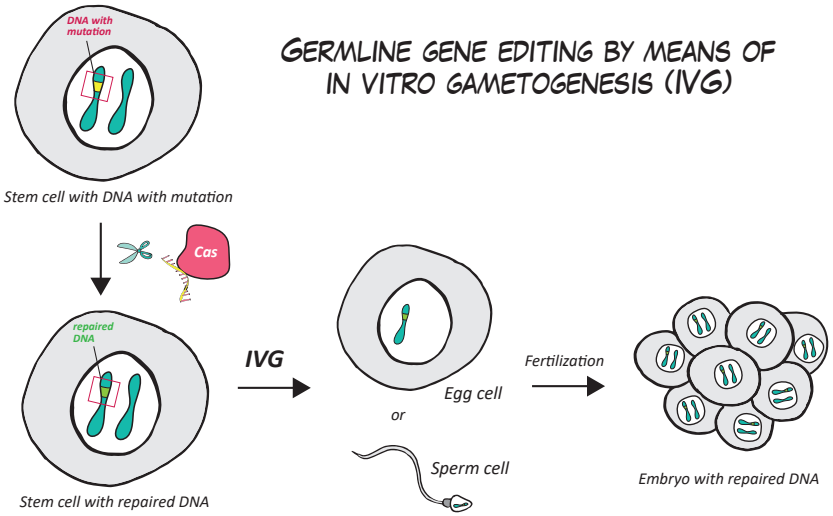

Figure 5 Germline gene therapy via IVG

Would you like to know moren about this subject?

- Invite us for a presentation or evening of dialogue on this theme.
- Do you have a personal question? Please contact the NPV Advice Line: call (0318) 54 78 88.
- Do you wish to know more? Go to www.npvzorg.nl/thema/kiembaanmodificatie.

List of concepts with definitions

- A **congenital disorder** or disease is a disorder or disease that the child has from birth. This can be hereditary or non-hereditary.
- A **congenital, hereditary disease** or disorder has to do with a mutation in the hereditary information that comes from the parents. Each child of those parents then has an increased risk of that abnormality. A congenital, **non-hereditary disorder** sometimes has to do with an abnormality in the hereditary information of the child, but that abnormality does not originate from (one of) the parents. Any subsequent children will then not have an increased risk of the same abnormality. Incidentally, a chromosome extra (such as in Down's Syndrome) can be both hereditary and congenital non-hereditary.
- A disease or abnormality is **dominant genetic** if one abnormal gene (from a gene pair) is already sufficient to cause the disease. One of the parents often has this disease. A well-known example is Huntington's disease. See figure 3 on page 9.
- A disease or abnormality is **recessive genetic** if this disease or abnormality only manifests itself when both genes of a particular gene pair are abnormal. See figure 3 on page 9.
- **Carriers** are those persons who carry one abnormal gene from a recessive hereditary disease. In that case, the disease is not expressed in them because they also have a "healthy" gene. This is only possible in recessive hereditary diseases. If one "carrier" marries another and the child gets the abnormal gene from both parents; in that case, the child will get the disease. Two "carriers" are more likely to marry each other in marriages between family members (cousins) and in smaller closed communities.
- **Embryo**: the very beginning of a baby, from conception until the unborn child is nine weeks old (that is, at eleven weeks of pregnancy). From that time, the unborn child is called a "fetus."
- **Gene**: a piece of hereditary information required for a certain trait.
- **Genetic**: what has to do with DNA can be called genetic. For example, genetic research is research into DNA. Genetic is not the same as hereditary. Some diseases, such as Down's syndrome, are related to DNA but are not hereditary.
- **Genome**: The genome of an organism is the set of hereditary information in a cell.

- **Gene therapy on body** cells (somatic germline gene therapy): cells from a patient with an abnormality in a particular gene receive a piece of DNA containing the healthy gene as a means of treating the hereditary disorder.
- **Sex cells**: egg cells and sperm cells. A sex cell has a set of unpaired chromosomes and a single sex chromosome. When the sperm and egg cells merge, the chromosome number is doubled.
- **IVF**: in vitro fertilization, the fertilization of an egg cell by a sperm cell in a well dish in the laboratory, test tube fertilization; treatment of infertility on the part of a couple.
- **IVG**: in vitro gametogenesis; this is the "culturation" of sex cells (sperm or egg cells) from other cells in a well dish in the laboratory.
- **Germline**: the group of cells from which the sex cells are ultimately formed. Other cells in an embryo will specialize and form cells each with its own function, also called somatic cells.
- **Germline gene therapy** or germline gene editing: therapy to treat an abnormal gene; correction of a mutation in the DNA of an embryo or in the sex cells that create an embryo. If this treatment succeeds, the abnormal gene will no longer be passed on to the offspring of that embryo.
- **Cultured embryo**: an embryo that is specially made for research purposes.
- **Body cells**: cells that make up all organs of the body. Cells with chromosomes in pairs.
- **Monogenic disorder**: a hereditary disease caused by a mutation in one gene.
- **Mutation**: a change in the order of building blocks in the DNA; this can change the hereditary information of that piece of DNA; sometimes this does not make much difference to the characteristics, sometimes the change is (very) harmful and there is a (serious) hereditary disorder.
- **Test tube fertilization**: see IVF.
- **Residual embryo**: an embryo that is "left over" and is not placed in the uterus after a test tube fertilization.
- **Trisomy**: The condition in which a person's cells contain three copies of a particular chromosome instead of two.
- **Zygote**: Fertilized egg cell, the beginning of embryonic development in a human.

For further reading

- Go to npvzorg.nl/thema/ to read more about IVF, embryo research, gene therapy and germline gene editing.
- The website erfelijkheid.nl provides explanation and information about heredity and hereditary disorders.
- Biowetenschap en Maatschappij [Bioscience and Society] (2019), biomaatschappij.nl/gentherapiebelofte/.
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