Supplementary Data 3. Background information provided on webpage after filling out the questionnaire

How far are we from genetic modification?

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What is already possible in terms of genetic modification and what may be coming? The Kennis van Nu explains it using five scenarios.

What does the Netherlands think about future possibilities of using genetic modification? That is something that reproductive biologist Sjoerd Repping of the Academic Medical Centre Amsterdam and the Kennis van Nu would like to know. That is why we designed the short questionnaire with five different scenarios. Do you wonder how far away each of these scenarios are? We explain this in the section below.

Scenario 1: You are gluten intolerant. Would you want to eat gluten-free wheat that was created by genetic modification?

Although gluten-free wheat does not exist (yet), wheat with so-called 'safe' gluten has been developed. These are gluten of which the genetic components are removed that are harmful for people who are gluten intolerant. Scientists have taken some significant steps forward in a number of recent studies.

According to the expert in plant technologies Jan Schaart in Wageningen, safe gluten are a very welcome solution: 'One or two percent of the population has a gluten hypersensitivity. But gluten are needed for, for example, baking quality bread and removing gluten altogether is unwise.' Furthermore, not just baking products and pasta contain gluten, but they are in binders that are used for ready-made soups and sauces, and are processed in many meat products'.

Still, safe gluten won't get into supermarkets very quickly: 'The wheats that are created so far are from transgenic plants (plants that contain genes from a different type of plants) and this is difficult to apply in practice. Regulations and acceptation among the general public are standing in the way', explains Schaart. 'We have to do many safety studies, which will take years and costs millions. We personally wonder how many of these are needed'.

New methods such as CRISPR-Cas may offer a solution. The European Commission is currently debating a regulatory exception for plants that have been created using CRISPR-Cas. These plants are initially transgenic, but after using CRISPR-Cas this element will be removed again. As such, these plants will eventually be similar to those that are made with more traditional methods. 'I think it will take about five years to develop wheats that are safe for most patients', says Schaart.

Scenario 2: You have a severe neuromuscular disease because of which you are likely to end up in a wheelchair. Would you want to genetically modify yourself to prevent this?

'It isn't possible to recover muscular damage that has already occurred by means of genetic modification', explains Annemieke Aartsma-Rus, professor in translational genetics at the Leiden University Medical Centre. Scientist are working on treatment using genetic modification to prevent progression of neuromuscular diseases. For example, they are working on Duchenne muscular dystrophy in mice.

Those who have this disease experience a progressive muscle weakness and frequently eventually die of heart problems. 'If you can stop or delay the progression of the disease, that would be a major step forward', says professor Regenerative Medicine at the Utrecht University and the Hubrecht Instute Niels Geijsen, who does research on this himself.

Still, Aartsma-Rus does not expect gene therapies for neuromuscular disorders to be applied in the clinics shortly. 'We have a lot of muscle mass (30–40% of our total body mass) and we expect these therapies need to reach more than 10% to have any effect.' Genetically modifying a single cell nucleus—which we can already do now—would be futile.

This is why Geijsen is working on treating specific body parts such as the arm: 'One could treat the muscles of the arm of an 18-year old patient, in order to allow him to independently operate his wheelchair.' A number of recent studies in Science show that scientists have been able to reach up to 20% of muscle mass in mice. 'We expect that this percentage will go up because of our research.' Still, the step from mice to human is still too large.

If you want to cure neuromuscular diseases, you have to treat in a very early stage. 'The problem is that you can only intervene once you know someone has the disease and for most neuromuscular diseases this won't become apparent until after birth,' according to Aartsma-Rus. 'The earlier you intervene, the bigger the effect one can expect. At best, this would be in an embryonic stage of development.'

Scenario 3: You have a heritable severe neuromuscular disease and you want to have a child. Would you want to genetically modify your embryo so that your child will not have this disease?

Because of innovative new genetic techniques like CRISPR-Cas, we are now able to alter DNA of organisms and embryo's. In animals, this has been applied successfully and thus far one study reports on modifying human embryos. These embryos have not been inserted into a womb and no children have been born after using these techniques.

'Before genetic modification of embryos is applied in the clinic, this technique needs to be safe and effective. It isn't now', according to Saskia Hendriks, researcher at the Academic Medical Centre Amsterdam. Not just Hendriks, but scientists all over the world share this perception.

In addition, it is legally not allowed to insert modified embryos into a womb and allow it to develop into a foetus. Furthermore, there are ethical reasons why scientists are not moving forward with these applications.

However, scientists are working to improve the genetic techniques such that these may one day be suitable for clinical applications. In theory, scenario 3 could be possible in the future, according to Hendriks: 'If the CRISPR techniques are sufficiently developed and we have an adequate understanding of the genetic basis of a neuromuscular disorder, we could modify the mutation that causes the disease, thereby preventing the disease'. This is of course only possible if the legal constrains of inducing pregnancies after the use of these techniques are lifted.

Scenario 4: You are healthy and you want to have a child. Would you want to genetically modify your embryo so that your child will be resistant to HIV?

There have not been many studies using human embryo's and everything that has being done is still in preclinical phases. However, in theory also this application of genetic modification may be possible in the future, according to Hendriks. Due to a specific genetic variation, some people have a natural resistance to HIV.

Using genetic technologies, one could copy this natural mutation and introduce it in an embryo, says Hendriks: 'however, this would require couples to become pregnant using IVF instead of naturally.'

This intervention is different from previous cases, as here the modification is aimed to prevent a disease which both the parent and the child do not (yet) have and of which it is uncertain if they would get it. 'Because there is less uncertainty about acquiring the disease, it has been argued this modification is less 'medically required' explains Hendriks.

Scenario 5: You are healthy and you want to have a child. Would you want to genetically modify your embryo so that your child will be more intelligent?

This scenario is still very far away. Studies show that intelligence is only partially determined by genes. 'Because intelligence is only in part genetically determined, we will never be able to fully determine someone's intelligence using genetic modification' according to Hendriks. As for the part of intelligence that is determined genetically, scientists do not yet fully understand which genes are involved. We need to better understand this before genetic modification becomes an option.

This final scenario takes things one step further. The goal is not to cure or prevent a disease, but enhancement. This makes the concept of 'the engineered human' come a bit closer. Do we want to, for example, be able to decide on the eye colour of our children or make sure that they have a predisposition for improved muscle growth? Such 'non-medical' interventions may also become possible in the future.

Scenarios like these compel us to ask ethical questions. Where do we draw the line? Who is going to bear the costs? In short, science needs to know what you think. Would you like to share your views and have you not done so already? We would be thrilled to hear your views though the short questionnaire.

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