

# Gene Therapy and Ethics: the Patient View

A tool for **patients** dialogue



## Colofon

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## Introduction

For some years now, gene therapy has been seen as a great promise for the treatment of several serious diseases. In particular, it has been seen as a route for the treatment of genetic disorders. Despite initial optimism and several promising early results, gene therapy has not yet delivered as many clinically available treatments as expected. However, the number of clinical trials for diseases open to gene therapy has increased rapidly. Most of these (potential) products are for cancers, with some of the most successful ones in the area of genetic disorders. For example, in the field of primary immunodeficiencies, gene therapy has already been shown to be a life-saving, life-extending treatment leading to dramatic improvements in health and quality of life. This gives substantial hope for future progress of treatment of many other genetic conditions.

Patients and patient organisations are amongst the keenest advocates for research and development in gene therapy. Their benefit is not in getting a scientific degree or title, earning money or even being on the news. Their benefit is in improving health and overcoming a life-threatening disease, in cure rather than care. Gene therapy has the potential to make a gene medicine possible and that potential is the drive for patients to promote and support gene therapy.

When it comes down to application of new insights and therapies, ethical issues start playing an important role. In particular for gene therapy that influences the basis of life: the DNA. Ethics come into view for example, when working out the necessary safety protocols, clinical trial setups and inclusion criteria of patients for research and treatment. This brochure aims to support dialogue within patients' communities on ethical questions related to gene therapy clinical trials.



## Is it necessary to develop a new concept of therapy with unknown risks when there are alternatives?

Many patients and their families consider gene therapy as a route to tackle the fundamental biological cause of their disorder: the faulty gene being replaced by a healthy gene. It might ultimately eliminate the need for complex services of integrated interventions, care and support, many of which often need to be lifelong.

Most genetic conditions are complex, multi-system disorders: they affect multiple organs in the body. To treat or prevent such a disease, an effective therapy would need to intervene broadly in all affected organs. Even where interventions currently exist, these are often demanding and of limited benefit for the affected person, e.g. the daily treatment regime for children with cystic fibrosis. Or interventions like bone marrow transplantation that are increasingly successful in some patients, might not be possible in other patients: without a suitable donor they will simply die.

For these patients it is therefore necessary to develop a new concept of therapy, even when it is still in its infancy and even when there are unknown risks: they don't have an acceptable alternative. Gene therapy offers a new perspective on life, on hope and on a future that can be full of plans, instead of living from day to day.

## Is gene therapy ethically right or wrong?

When is something 'ethically acceptable to do' and when do we consider something as ethically wrong? Where are the boundaries and who sets them? This is a crucial, but in itself also rather difficult problem. We can say that something is ethically 'right', when we do 'good'. But when do we consider something as a good act? Numbers of famous philosophers have discussed this subject more thoroughly than we can do so here, but what is evident is that we need criteria.

In the tradition of the philosopher Kant, the criteria to consider gene therapy as an ethically 'good' development, is to question whether we use patients as a goal or as a tool. Rather than use patients as a tool just to do research on gene therapy, patients should be seen as a goal: their wellbeing is at stake, not their role in research itself. Their interest is the outcome, not the process. In this respect, it is ethically right to develop new research.

## When is it safe enough to move from animal studies to clinical trials?

This is always a difficult issue. Animal models never completely match the human disease situation and species-specific differences for the safety and efficacy assays might exist. Protocols of research groups and coordinating supervising organisations such as ethical commissions of academic research centres and the European Medicine Agency determine the right moment for clinical application. Patients have great confidence in these protocols.

However, especially in the case of life-threatening, progressive diseases, patient organisations underline the need for quick evaluation processes. Scientists report that bureaucratic processes often delay research developments, much to the disappointment of patients. In the case of gene therapy, the research protocols should be continuously evaluated to perceive opportunities for standardisation and simplification. Best practices and new insights should have an effect on protocols as soon as possible.

## **H**ow to deal with pediatric patients taking part in clinical trials?

Up to now, only children who are seriously ill or have illnesses incurable by conventional means have been involved in clinical trials using gene therapy. For those with serious illnesses that aren't responsive to conventional therapies, gene therapy may offer hope that didn't exist only a short time ago. However, questions about the safety for the patient are raised in the case of gene transfer in very young patients for rare diseases in which there are no other efficacious treatments. This is especially important for life-threatening, progressive diseases, where no adult patients are available.

Special consideration is needed to identify the stage of the disease where gene therapy is hoped to be effective. The value of a trial in terms of putative benefit, i.e. efficacy of the treatment, will often have to target very young children.

Especially in those cases involving pediatric patients, collaboration with patient organisations is of importance. They have expertise in how to deal with informed consent and getting into contact with parents and their children. Children cannot give informed consent as consent implies a full understanding of the potential risks and other considerations of a clinical trial, an understanding which may be beyond the child's intellect. However, children should be heard on their 'assent' or 'dissent'.

## **I**s somatic gene therapy more or less ethical than germ-line gene therapy?

Somatic gene therapy involves introducing a 'good' gene into the patient's cells to treat the disease, but it won't change the chance that the disease will be passed on to the patient's children. The procedure may have to be repeated in future generations. This is the more common form of gene therapy being done.

Germ-line gene therapy involves modifying the genes in egg or sperm cells, which will then pass any genetic changes to future generations. Although it has potential for preventing inherited disease, this type of therapy is controversial. Germ-line transmission of an undesirable trait could nowadays be prevented by pre-implantation genome diagnosis, and germ-line gene transfer then remains open only for enhancement, which is considered unethical.

However, in the practice of chemotherapy and clinically indicated irradiation, unintended germ-line genomic changes cannot be excluded and are even expected (semen is often collected and banked before such treatments). Thus with any somatic cell therapy that is systemic, germ-line changes could be an unavoidable consequence. In these non-gene therapy situations the risk is apparently taken, whereas in experimental human gene therapy the issue of putative germ-line gene transfer, i.e. genetic modification, receives more emphasis in evaluating the risk/benefit ratio.

## **D**o gene transfer clinical trials with genomic insertion always require a long-term follow-up?

Patients are willing to cooperate in safety protocols, but these should have a legitimate basis. There should always be an extensive evaluation of the risks and benefits. Long-term follow up will be necessary in many cases, both for a person's health and for scientific reasons.

## **H**ow to deal with viral gene and transgene shedding?

Patients have the same goals and interests regarding safety as society in general and this counts for shedding issues as well. Shedding is documented as environmental spreading of the viral gene or transgene via excreta (urine, faeces, sweat, saliva, skin, semen) and blood. Patients want to protect their families and friends from potential hazardous effects of shedding. The risks of shedding should be evaluated thoroughly but also pragmatically. There should be a balance between risk management and quality of life of patients. Life-long screening programmes should have a scientific basis and otherwise lower regimens of control should be chosen.

## **H**ow can patients help scientific research?

Patient organisations are relevant partners in setting research agendas in a meaningful, societal context. Patient organisations do not wish to take away the intellectual freedom of scientists when they make choices in prioritising research questions, but they want to add their perspective in order to make the research relevant and to make visible the need for certain research paths. Patient organisations can help researchers find funds and gain society's approval and support.

## **H**ow to obtain a valid informed consent?

When asking patients for their informed consent to participate in clinical trials, it can be very helpful to consult patient organisations in advance. They can give insight into the available knowledge amongst patients and can help to make sure the patients are fully informed when they give their consent. This can avoid later problems.

Patient organisations can also evaluate informed consent forms to make sure they are complete and meet ethical standards. This will not only increase transparency, but will result in a greater trust that the system is working well for participants. It is important to remember that without the patient's willingness to participate, gene therapy will never become a cure or true gene medicine.

## **W**hat are the regulations for participants? Are they too rigid or too loose?

Regulations on clinical trials are applied by governments to minimise risks for people taking part. Any gene therapy that looks like it is going to work will have to be licensed by the relevant competent authority. The European Commission has introduced the Advanced Therapies and Tissue Engineered Products Regulations. Patient organisations played a key role in persuading the European Parliament and the Council of Ministers of the importance of these legislative proposals.

Issues such as 'age of consent', 'failure of currently approved standards of care' and 'life versus quality of life' are ethical principles applied in regulation. They are sound principles to protect patients from undue risks. However, sometimes it is necessary to loosen these principles in order for the patient to experience the greatest benefit. For example, to enter clinical trials, existing treatments must fail and patients need to have progressed to advanced stages of the disease, but probabilities of success are sometimes likely to be higher when patients can enrol earlier.

Too rigid implementation of the ethical principles imposed by law can unnecessarily obstruct the already long road for gene therapy. The patient is the one who can connect with the effects of new

developments in gene therapy most easily. He will set his boundaries lower, will be more enthusiastic and willing to take more risks; what does he have to lose anyway? Regulations should be based on responsibility towards the patient and on his quality of life.

## **S**hould information on clinical trials be made public?

A central database for all clinical gene therapy trials should help to decide on why a new trial should start and how. The rationale for a database with information on gene therapy clinical trials is based on the right of all patients, clinicians, the research community and the tax payers to know about these trials. A central databank that is transparent and public is important to gene therapy's acceptance.

Trial results are usually published in journals, but often only positive results of completed trials are published. However, negative results are equally important, since one can learn from these findings as well. A database including all valid trial results, positive and negative, is thus necessary for sharing information and maximising knowledge to speed up the development of safe gene therapies. It is important that such a database clearly states why a result has been deemed either positive or negative so as to not mislead the public.



## More info

For more information on patient organisations involved in gene therapy:

- \* European Genetic Alliances' Network EGAN: [www.egan.eu](http://www.egan.eu)
- \* European Organisation for Rare Disorders Eurordis: [www.eurordis.org](http://www.eurordis.org).

This brochure can be downloaded from [www.egan.eu](http://www.egan.eu) and [www.biomedinvo4all.com](http://www.biomedinvo4all.com).

Also available: Gene Therapy and Ethics: the Patient View. A tool for Public Dialogue.

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- \* The Netherlands Organisation for Health Research and Development ZonMw: [www.zonmw.nl/en/](http://www.zonmw.nl/en/).



- \* The Dutch Genetic Alliance VSOP: [www.vsop.nl](http://www.vsop.nl).

