Gene Therapy: Living With(out) Haemophilia?

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Disclosure:	The author has declared no conflicts of interest.
Received:	08.04.25
Accepted:	04.06.25
Keywords:	Cure, ethics, gene therapy, haemophilia.
Citation:	EMJ Hematol. 2025;13[1]:90-93. https://doi.org/10.33590/emjhematol/QMQG5189

INTRODUCTION

Since research on human gene therapy began, the expectations regarding its potential in treating haemophilia have been high. Haemophilia is a heritable bleeding disorder, characterised by a lack of clotting factor VIII (in the case of haemophilia A) or IX (in the case of haemophilia B). As a result of this deficiency, people living with haemophilia experience spontaneous and trauma-induced bleeding into muscles and joints, which can lead to pain, arthropathy, and loss of function. At this moment, multiple treatment options for haemophilia are available, which allow people living with the condition to have an increasingly normal lifespan and quality of life.[1]

However, none of these treatment options have led to a definitive cure for haemophilia. Therefore, the field has focused on gene therapy to bridge this gap. At the time of writing, three gene therapy products for haemophilia have received market authorisation by the European Medicines Agency (EMA), and more products are under development. Results from trials indicate that these gene therapies are effective and increase clotting factor levels, thereby decreasing the number of bleeding episodes and foregoing the need for prophylactic treatment.[2] However, some studies indicate that these effects decrease over time, and it is unknown how long clotting factor levels will remain elevated, as there is still a scarcity of long-term follow-up data.[2] As a result, there is no consensus on whether gene therapy has already led to a cure, or if it will be capable of producing a cure.[3]

Due to these uncertainties, people who have received gene therapy may not be described best as living with haemophilia, nor as being cured from haemophilia.

IN BETWEEN HEALTH AND DISEASE

The state of being in between health and disease has already been described in the literature, both for people who no longer have a disease and for people who do not yet have a disease. The first group is said to be 'in remission' after active medical treatment.[4] The second group is described as being 'in waiting' after receiving a diagnosis, but before the onset of symptoms.[5] Paradoxically, gene therapy can lead to a state in which people living with haemophilia simultaneously find themselves both 'in remission' and 'in waiting'.

To begin, the term 'remission society' has been used to describe all people who have had a disease and are effectively well, but who still experience consequences of the disease.[4] According to Arthur Frank (VID Specialized University, Oslo, Norway), a sociologist and cancer survivor who

introduced the term 'remission society', this includes all those with a history of illness. This group consists of, but is not limited to, cancer survivors who are not declared 'cured' because the cancer might return at some point in time, all people who have to return to the doctor for a check-up, or people with a pacemaker that offsets the metal detector at airports.[4]

When gene therapy for haemophilia achieves the effects that are aimed for in trials (i.e., long-term increase in coagulation factor levels, thereby foregoing the need for clotting factor replacements) people will no longer have any symptoms of haemophilia. However, they will continue to live with the consequences of haemophilia. This may include joint damage that will continue to progress, potential psychological burdens, and any other consequences that have resulted from haemophilia, such as career opportunities that were lost earlier in life. Furthermore, as haemophilia is a congenital disorder, it will remain a factor to take into account when making reproductive choices for people who have been 'cured'. As a result, haemophilia will continue to have an impact on their lives, and they may not be able to live with a completely "haemophilia-free mind".[6]

Meanwhile, the notion of "patients-in-waiting" is used to describe people who are already diagnosed with a disease, but do not (yet) experience symptoms. This includes, for instance, infants who receive a genetic diagnosis or people who receive a biomarker-based diagnosis, such as for Alzheimer's disease, before the disorder becomes symptomatic.[5,7] The term is also used to describe people who are at risk of developing a disease, such as people with high cholesterol.[5] These people are described as being in a diagnostic 'limbo', wherein they have received a disease label, but it might be years before they start experiencing the first symptoms, if ever.

Results of gene therapy trials for haemophilia seem to indicate that, for many individuals, gene therapy is effective in reducing, and in some cases fully eliminating, symptoms. This allows people to live a life free of bleeding risk after gene therapy. At the same time, these effects appear to decrease over time.[2] However, the likelihood and timing of this decrease remains hard to predict, as there is still a scarcity of long-term follow-up data, and the data that does exist indicates that there is much variation between individuals.[2] As a result, it is hard to predict if and when people may need to return to prophylactic treatment after gene therapy. This puts people who have been treated with gene therapy in a position similar to that of "patients-in-waiting"; there is a chance that the disorder might return in their lifetime, but it is uncertain if this will happen and, if it does, when symptoms will reoccur.[5,7]

People living with haemophilia differ from the groups traditionally described as 'in waiting'. Not only have they been diagnosed with haemophilia at a young age, but they have also experienced symptoms and needed continuous treatment from the moment they learned to crawl. Nonetheless, because of the promise of being cured and the expectation that they will be permanently relieved of haemophilia, they share the characteristics of "patient-in-waiting".

Therefore, gene therapy might lead to a group of people who are not best described as living with haemophilia, nor as being free from haemophilia. Instead, a new group arises: people living both with and without haemophilia, who live with an uncertainty about their future well-being.

ETHICAL CONSEQUENCES

There are several ethical consequences regarding this uncertain state. To begin, people may need to cope with uncertainty and fear for their future health and well-being. Qualitative research indicates that, for some people who participated in a gene therapy trial, seeing their clotting factor levels go down created stress, as they started to worry about the moment the effects would disappear and they would need to return to prophylactic therapy.[8,9]

This state also raises questions about what medical care is suitable and appropriate. For some people living with haemophilia, being cured might entail being free from doctor's appointments and medical check-ups. However, regular check-ups may be necessary to monitor how the person is doing and if their clotting factor levels are still sufficiently high. Moreover, participation in follow-up research is highly desirable to obtain knowledge about the long-term effects of gene therapy, which is required to allow people living with haemophilia to make informed treatment choices in the future.

Additionally, awareness of this "in-between" state is essential for decision making regarding gene therapy. This outcome is different from the way gene therapy is often portrayed, i.e., as a definitive cure for haemophilia. This discrepancy may lead to unrealistic expectations of gene therapy, which could impact the informed decision-making process. The difference between expectations and reality of a 'cure' after gene therapy may occur for people living with various disorders and conditions. However, the issue is particularly salient for haemophilia. There are already several treatment options available for haemophilia; thus, opting for gene therapy (if available to the person in question) is a choice rather than a necessity, which contrasts disorders for which no or very few other treatment options are available. The choice of a certain treatment option may, therefore, depend on its effects on quality of life, as well as personal preference.

These ethical consequences require attention from the medical community. To begin, the psychological distress that may occur requires appropriate care and support. Other authors have already argued for the importance of offering psychosocial care to people undergoing gene therapy.[8] In providing this care, there should be a focus on realistic expectations of what life will look like after gene therapy and the uncertainty surrounding the long-term effects of the therapy.

Furthermore, when discussing gene therapy with people living with haemophilia, healthcare providers might consider using a term other than 'cure' to describe the expected outcome of gene therapy. The notion of a cure is likely to elicit expectations of life-long effects, which may be unrealistic. Instead, choosing words that more concretely describe the effects of gene therapy may allow people to make a more well-informed treatment decision.

CLOSING REMARKS

To a certain extent, reaching this state in between health and disease is inherent to gene therapy; haemophilia will remain a congenital disorder, which can be passed on to future generations, and joint damage that has been incurred before will not disappear. Yet, a part of this uncertain state may be temporary. For instance, because of the improved standard of care for haemophilia, younger generations will incur less joint damage, and thus will have a smaller burden of being "in remission" than older generations, who have not always benefitted from this standard. Furthermore, as the amount of follow-up data from gene therapy increases, we may be able to better predict how long the effects will last. Moreover, in the developmental process of gene therapies, a product may be developed with a more stable and longer-lasting effect, thereby decreasing the uncertainty about the return of haemophilia (symptoms). Nevertheless, at this moment, the outcome of being 'not entirely with haemophilia, nor entirely without' after gene therapy is an important consideration for people living with haemophilia who are choosing between various treatment options.

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