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REVIEW ARTICLE

The ethics of gene therapy for hemophilia: a narrative review

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Abstract

Gene therapy is expected to become a promising treatment, and potentially even a cure, for hemophilia. After several years of research, the first gene therapy product has been granted conditional market authorization by the European Union in August 2022. The recent progress in the field also has implications on the ethical aspects of hemophilia gene therapy. Reviews conducted in the 2000s mainly identified questions on the ethics of conducting early-phase clinical trials. However, since then, the knowledge on safety and efficacy has improved, and the field has moved toward clinical application, a phase that has its own ethical aspects. Therefore, we conducted a narrative review to take stock of the ethical aspects of hemophilia gene therapy. Based on our analysis of the literature, we identified 3 ethical themes. The theme *Living up to expectations* describes the existing hopes for gene therapy and the unlikelihood of the currently approved product becoming a permanent cure. In the theme *Psychosocial impacts*, we discuss the fear that gene therapy will impact the identity of people with hemophilia and their need for psychosocial support. The theme *Costs and access* discusses the expected cost-effectiveness of gene therapy and its implications on accessibility worldwide. We conclude that it may be necessary to change the narratives surrounding gene therapy, from describing it as a cure to describing it as one of the many treatments that temporarily relieve symptoms and that there is a need to reevaluate the desirability of gene therapy for hemophilia, given the availability of other treatments.

KEYWORDS
ethics, gene transfer techniques, genetic therapy, hemophilia A, hemophilia B

1 | INTRODUCTION

Gene therapy is seen as a promising treatment, and potentially even a cure, for various congenital disorders. Already in the early 1990s, hemophilia was identified as the ideal test case for validating gene therapy principles because it is a monogenic disorder with a wide therapeutic window and its effect, ie, an increase in clotting factors levels, is easily measurable [1,2]. Three decades later, in August 2022, the first gene therapy product for hemophilia A, Roctavian (valoctocogene roxaparvovec), was granted conditional market authorization in the European Union [3]. The product is a form of adeno–associated virus (AAV)–mediated gene transfer—a technique in which a

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substitute copy of the gene coding for the missing clotting factor is delivered to the liver by the means of a recombinant nonintegrating AAV vector, with the intention of achieving sustained clotting factor levels in the normal range [4]. The development of gene therapy for hemophilia has thus far mostly focused on AAV–mediated gene transfer. In addition, several other gene therapy products and techniques are being researched and developed for both hemophilia A and B.

Gene therapy not only offers a potential for improved treatment but also raises ethical issues. A distinctive characteristic of gene therapy trials compared with other types of trials is the high level of complexity and uncertainty [5]. Furthermore, because AAV-mediated gene therapy cannot be repeated, people who participate in the early-phase trials will likely not be eligible to receive a potentially more effective gene therapy later [6]. Reviews conducted in the 2000s mainly identified questions on the ethics of conducting clinical trials, chiefly regarding the risk-benefit ratio and the inclusion of children or people living in low-resource settings [7,8]. However, since the publication of these reviews, there has been much progress in the development of gene therapy strategies for hemophilia, particularly in AAV–mediated gene transfer techniques. As a result, the knowledge of its safety and efficacy has improved, and the field has moved beyond the early-phase trials and toward clinical application. This new phase has its own ethical aspects. For instance, market introduction of expensive treatments may create challenges surrounding access and reimbursement [9].

Because these new developments have ethical relevance, we conducted a review to take stock of the current ethical aspects of hemophilia gene therapy. Gaining insights into the ethical aspects of novel treatments throughout all stages of development is essential to be able to constructively guide the technology to a responsible introduction into society [10].

2 | CURRENT HEMOPHILIA TREATMENTS

Hemophilia is an X–linked congenital bleeding disorder. Owing to a lack of clotting factor VIII (FVIII, hemophilia A) or IX (FIX, hemophilia B), persons affected with a severe form of hemophilia suffer from spontaneous and trauma–induced bleeding into muscles and joints, resulting in chronic pain and loss of function [4,11]. Severe hemophilia affects around 1 in 10.000 men worldwide [12].

Currently, hemophilia can be managed by several types of treatments. Clotting factor replacement therapy allows to relieve the heavy burden of disease for most persons with hemophilia, but they also have several drawbacks: people may form inhibitors to the administered factors, the intravenous injections are burdensome, and the treatment is expensive. Because of the high costs, around 70% of people with hemophilia worldwide do not have access to adequate care [13]. In recent years, treatment options have expanded with the introduction of products with an extended half-life, thus requiring fewer intravenous injections, for both hemophilia A and B [14], and emicizumab for hemophilia A, a nonreplacement therapy that requires lower frequency and subcutaneous, instead of intravenous, injections [15].

Essentials

- The first hemophilia gene therapy has reached the market but it also raises ethical issues.
- We conducted a narrative review to gain insights into and evaluate the ethical landscape.
- We identified the themes *Living up to expectations*, *Psychosocial impacts*, and *Costs and access*.
- It is necessary to change the narrative of gene therapy as cure and to rethink its desirability.

3 | METHODOLOGY

We started with a systematic review, searching PubMed, Embase, and Web of Science for relevant articles in November 2021. Based on our findings, we concluded that a systematic search could not capture all relevant literature because (1) we are looking for a wide spectrum of ethical aspects, which are hard to capture all with a single search string, and (2) relevant ethical aspects are often discussed in articles that primarily focus on other topics than hemophilia gene therapy because many of the ethical aspects are not unique to gene therapy and/or hemophilia but also occur for other types of translational and regenerative medicine. Therefore, we changed the design to a narrative review, which allowed us to include a wider spectrum of publications. In addition to the articles found in the initial search, we included articles through snowballing, articles that were suggested to us by experts in the field, and we included seminal articles on specific ethical topics that we identified throughout our analysis. The original search strings for each of the databases can be found in the supporting information.

4 | ETHICAL THEMES

Based on our analysis of the literature, we constructed the following 3 ethical themes: living up to expectations, psychosocial impacts, and costs and access. Each will be described in more detail below. An overview of the ethical aspects discussed can be found in table 1.

4.1 | Living up to expectations

Many authors, particularly those writing in the early 2000s, express the hope that gene therapy will eventually cure hemophilia [16–21]. Another expected advantage of gene therapy is its potential to circumvent many of the downsides of standard factor replacement therapy, such as the impact on quality of life, high costs, inhibitor

TABLE 1 Ethical aspects of hemophilia gene therapy.

Theme	Ethical aspects
Potential to live up to expectations	• Gene therapy raises FVIII and FIX levels, but its effects appear to decrease over time • Gene therapy is unsuitable for several people with hemophilia, including children, people with inhibitors, people with liver damage, and people with pre-existing antibodies • The improved standard of care for hemophilia has heightened the expectations of gene therapy • There are risks of side effects that may require treatment with immunosuppressive therapy • The informed consent process should be elaborate in a treatment setting as well because of the remaining uncertainties and no possibilities to discontinue gene therapy after it has been administered
Psychosocial impacts	• Becoming symptom free may cause the experience of the burden of normality • The decrease in effects of gene therapy may create anxiety and require psychosocial support • Loss of hemophilia identity may decrease solidarity within the (global) hemophilia community
Costs and access	• It is expected that gene therapy will be cost-effective, but uncertainties remain • The expected costs create a risk for health care systems • Because of the availability of safe and effective treatment options, the principle of nonabandonment has less moral weight • The expected costs may widen the treatment gap between low- and high-resource settings

development, and the difficulty of venous access in small children [7,22].

Recent research indicates that AAV–based gene transfer therapies can indeed raise FVIII and FIX levels to a normal range, with the effects lasting several years [23,24]. Most trials for gene transfer products for both hemophilia A and B have resulted in a decrease in the number of bleedings and the need for prophylactic treatment [24]. At the same time, long-term follow-up data are still limited, and FVIII expression appears to decrease over time, causing some commentators to conclude that the therapy might only provide a temporary cure [24,25].

Furthermore, there are several groups of persons with hemophilia for whom gene therapies currently being tested are likely ineffective. The current products are not suitable for children with hemophilia and are probably ineffective for people with inhibitors, as a result of which they are excluded from most trials [24,25]. People with liver disease, which is prevalent in the hemophilia population because of the historic exposure to HCV–infected blood products, are also excluded from trial for the current liver-directed products. In addition, gene therapies that use viral vectors are unsuitable for people who have antibodies against the vector used. The prevalence of neutralizing antibodies ranges from 15% to 60% of the population, differing geographically and per AAV serotype [26]. Furthermore, because other novel therapies have improved the standard of care for hemophilia during the past few years, some expect that many patients will prefer these other treatment options over gene therapy [27]. These challenges have been described as discrepancies between hopes and reality of gene therapy for people with hemophilia [28].

Although the durability of the effects of gene therapy is now being questioned, other hopes for gene therapy have increased. According to Leebeek and Miesbach, the results of phase 1/2 trials have elevated the expectations of both the patients and physicians. Although the goal had originally been to achieve factor levels that prevent spontaneous bleedings, the current ideal is to achieve factor levels in the normal range [24]. Similarly, several authors express the hope that gene therapy will become available for people with moderate hemophilia, a group that mostly does not experience spontaneous bleedings and would therefore only benefit from higher factor levels [28,29].

Furthermore, there are new insights regarding the risks of gene transfer. Literature from the 2000s already described several theoretical risks of gene transfer therapy, mainly insertional mutagenesis, germ-line transmission, immunogenicity, and inhibitor formation [8,22,30–32]. The most serious concern based on the recent data appears to be the increasing liver transaminases, for which patients require immunosuppressive therapy [23,24,33]. In the phase 3 trial of the product that has recently been approved, 85.8% of participants had elevated aminotransferase levels that had to be treated with glucocorticoids [23]. Several trial participants and their family members reported that the immunosuppressive therapy they received during trial participation, either prophylactically or to treat a transaminitis, was the worst part of their trial experience, and some would only consider ever having gene therapy again if they could be certain immunosuppression would not be necessary [34]. Furthermore, several groups of authors warn that contrary to what is generally believed, AAV vectors do sometimes integrate [14,33,35]. They argue that this risk of integration requires more attention because the risk of oncogenicity is relatively high for diseases with a long life expectancy such as hemophilia [33].

Simultaneously, it is clear from the literature that there is a hope that other forms of gene therapy will be more effective, such as gene transfer strategies using a lentiviral vector or lipid nanoparticles, gene therapies through stem cell therapy, or gene editing technologies. However, these techniques are still in the earlier, mainly preclinical, stages of development than AAV–based gene transfer [15,36].

The updated insights on the benefits and risks also have implications for the informed consent process for gene therapy trials and treatment. Older research already raised concerns about the level of

understanding the potential participants have about the nature and aims of gene therapy trials [7,8,37–39]. Recent literature also emphasizes the importance of the informed consent process in a treatment setting, emphasizing that this too should be a process rather than a single event [34]. Fully understanding the goals of gene therapy and the risks and uncertainties surrounding it is considered particularly important because once administered, the vector with the gene therapy product cannot be discontinued [34,40]. To tackle these difficulties in informed consent, some argue that the information process about gene therapy should begin in childhood and continue throughout life to facilitate a well-informed decision [34,41].

4.2 | Psychosocial impacts

Some empirical articles describe the concerns by people with hemophilia about the impact of gene therapy on their identity. Some people with hemophilia fear that gene therapy removes a part of their identity of being a person living with hemophilia, and for some, this is also a reason to not want gene therapy [42,43]. Fletcher et al. hypothesize that this loss of identity feared by people with hemophilia may be because of the loss of the diagnosis of hemophilia and refer to the literature describing the "burden of normality." The burden of normality has mainly been described for deep brain stimulation as a treatment for epilepsy or Parkinson's disease. It describes the phenomenon of patients having to adjust to a symptom-free life after their treatment [44]. In these cases, the burden of normality does not result from the side effects of psychosurgery, such as mood disturbances, but from the psychological experience of becoming symptom free [44,45].

This is one of the examples that shows that concerns about the impact on personal identity resulting from a change in health status are not uncommon, although the topic may be new in the debate on hemophilia gene therapy. Similarly, people who have just been diagnosed with a chronic illness sometimes struggle to adjust to their new identity [46,47]. Because hemophilia is a congenital disorder that has a large impact on affected persons' lives [48,49], it is imaginable that a similar renewed identity may be experienced when they are cured. Research on the burden of normality has also shown that the experience of self-change is more severe for people who experienced their first disease symptoms before or during adolescence than for people who had experienced the first symptoms in adulthood [50].

In all these examples, the threat to personal identity is described as being the result of a "biographical disruption," in which people cannot integrate an event into the personal story they tell about themselves [46]. Personal identity is thus conceptualized in a narrative sense, which defines identity as "selfhood […] essentially tied not directly to the defining traits but to our ability to understand ourselves and others in narrative terms" [51, p. 136]. Within philosophical literature, however, there is discussion about how personal identity should be understood. Traditionally, personal identity is conceptualized as a set of core psychological characteristics that together make up the self, according to which the identity can be threatened if these core characteristics are affected [51]. When personal identity is understood in relational or narrative terms instead, a threat to identity occurs when people cannot integrate their experience of becoming symptom free in the story they (implicitly) tell about themselves and their life. Based on this narrative account, there is disagreement between authors whether the burden of normality as experienced by patients treated with deep brain stimulation is in fact a threat to personal identity [44,51,52].

To our knowledge, there are no reports of people with hemophilia who experienced a change in their identity after participating in a gene therapy trial. Therefore, it remains uncertain whether and how a change in identity will be experienced in practice, in particular because gene therapy may only provide a temporary rather than a lifelong "cure." However, it has been described that difficulty with psychological adjustment can occur in both the short and long terms after treatment [51], which gives a reason to not exclude the possibility of similar experiences for people with hemophilia, even if gene therapy only works temporarily.

Simultaneously, there are reports of trial participants who wished that there had been more attention for psychosocial aspects throughout the process and patients who felt that they lost control over their situation because of the trial procedures [34]. Furthermore, some trial participants expressed experiencing anxiety about the uncertainty concerning the duration of the effects and said that psychological support might be required when the effects decrease [34]. In addition, several authors argue for the importance of providing psychosocial support to people with hemophilia receiving gene therapy in a trial or as a treatment [13,29,33].

A potential change in identity has several ethical consequences. Most importantly, the burden of normality changes the risk-benefit ratio of a treatment because such changes in identity may be undesirable to patients [44]. To address this problem, some argue that patients and their families should be helped to construct self-narratives that allow for such a change in health status and should be thoroughly informed about the potential occurrence of this challenge [44,51]. Furthermore, participants in a round table discussion expressed the concern that the expected loss of hemophilia identity, in combination with a decreased importance of the hemophilia treatment center after gene therapy, may lead to the hemophilia community becoming less important. As a result, there were concerns that the solidarity within the community might decrease, in particular between people who have access to gene therapy and those who do not [13].

4.3 | Costs and access

It is expected that gene therapy products will be very expensive when they enter the market. The first licensed gene therapies for other disorders have been priced at $400,000 to $1.4 million per treatment [9]. Such a high price tag raises concerns about accessibility and how the treatment should be financed. Nonetheless, several studies have estimated that gene therapy for hemophilia will be cost-effective in

comparison to both intravenous and subcutaneous prophylactic treatments [53–55]. However, some uncertainties remain. Long-term follow-up data regarding efficacy and safety are still lacking, but current estimations have assumed an efficacy of 5 up to 10 years [53,55]. Calculations of cost-effectiveness are also hampered by opacity about the actual price that is paid for the current prophylactic treatment [53]. Because of the importance of obtaining data on long-term safety and efficacy, long-term, potentially lifelong, follow-up of people receiving gene therapy will probably be required [22,33,37,56].

The high costs in combination with remaining uncertainty regarding cost-effectiveness creates considerable risks for health care systems and raises questions about what societies should be willing to spend. Because of these uncertainties, there has been discussion about installing alternative payment models, which allow for risk-sharing arrangements between payers, providers, and manufacturers [57,58]. In discussions on the payment for such novel therapies, it is important to consider that in the resource-rich settings, hemophilia is no longer a life-threatening illness. For instance, with the currently available treatments, people with hemophilia in the Netherlands have a life expectancy that is close to that of the general male population [59].

Payment for the development or reimbursement for the use of expensive medications for rare diseases raises an ethical dilemma. On one hand, investing large amounts of money into rare conditions will only benefit a small number of people and create opportunity costs for society, in terms of benefits lost for others. On the other hand, there is a moral obligation to not abandon individuals with a rare condition [60]. In most ethical discussions surrounding the dilemma of allocating scarce resources for rare diseases, the principle of nonabandonment or the "Rule of Rescue", which is an imperative to save people who are in immediate danger, is invoked because there is no treatment available for many of these rare diseases, creating a large unmet need for the affected patients [60,61]. It has therefore also been argued that when making policy decisions regarding reimbursement of expensive medication, it is the severity of the disease that should be a guiding principle rather than its rarity [61]. However, because there are currently alternative treatments available for hemophilia and further treatments are being developed, the principle of nonabandonment and the Rule of Rescue lose some moral weight.

By contrast, it is estimated that around 75% of people with hemophilia worldwide do not have access to treatment. Therefore, some authors argue that gene therapy, which is expected to be a one-time curative treatment, might be a solution [20,27]. The World Federation of Hemophilia has also embraced gene therapy as a potential source for achieving its goal of "treatment for all" [13]. At the same time, these hopes appear to be based on the disputable expectation that gene transfer will provide a permanent, cost-effective cure with a single injection. Furthermore, some authors point out that diffusion of health innovations to low-resource settings has occurred with varied success in the past and that long-term follow-up, as advised for gene therapy, can pose a challenge in low-resource settings [28]. As a result, there is a risk that gene therapy widens the treatment gap between high-resource and low-resource settings.

5 | DISCUSSION

This narrative review has shown that different ethical aspects of hemophilia gene transfer have become prominent now that the technique is closer to the market. These include the therapy's potential to live up to hopes and expectations, its psychosocial impacts, and questions regarding costs and access. There is a considerable chance that gene therapies that will enter the market soon are not the once-in-a-lifetime permanent cure for hemophilia they were hoped and expected to be but rather a temporary treatment that alleviates symptoms, possibly with burdensome side effects. The treatment may also create psychosocial challenges that require support. Current literature suggests that such support may be both necessary in the scenario where the effects of gene therapy fade away over time because people would need support dealing with that uncertainty and in the scenario where gene therapy turns out to be a cure because people would have to adjust to a life without the symptoms of hemophilia. Finally, gene therapy will likely be very costly and can thereby create a burden for health systems and may not be a solution for those people with hemophilia in low-resource settings who currently do not have access to treatment.

These insights call for a reevaluation of the desirability of gene therapy for hemophilia. Almost 20 years ago, when the development of hemophilia gene therapy was still in the stage of early-phase clinical trials, some authors already raised the question whether the hemophilia community should be willing to volunteer itself as a model for gene therapy development, considering that there are other treatments available [30]. Since then, other treatment options have also developed further, alongside gene therapy. However, the choice a person has among treatment options depends on several factors, including whether they are afflicted with hemophilia A or B and whether they have inhibitors [4,15]. As a result, gene therapy may be more valuable for some people with hemophilia than for others.

Furthermore, these insights also suggest that a different narrative surrounding gene therapy may be more appropriate. Currently, the literature mainly describes gene therapy's potential to be a "cure" and the extent to which it has reached that goal or not. The current narrative of a cure is also amplified by the media, for instance through an article by the BBC describing the results of a phase 1 trial for hemophilia B as a "transformational breakthrough cure" [62], after only having data of 10 participants up to 26 weeks after gene transfer [63]. Instead, it appears that gene therapy will become one among the several treatments available for hemophilia that relieves symptoms for a certain period of time.

The possibility that gene therapy will only provide temporary relief of symptoms does not automatically make it invaluable as a treatment. However, it does mean that several of the arguments that were used in favor of the development of gene therapy, such as its ability to provide a cure, the possibility to overcome the global treatment gap, and its value for preventing joint damage in children [8], are very likely no longer applicable, as this review has shown.

In further search for a more permanent cure, researchers are no longer solely focusing on AAV–mediated gene transfer techniques but

have also started to include other gene therapy strategies that are expected to have a greater potential to become a cure than AAV–mediated gene transfer. Because such other forms of gene therapy are also being pursued, ethical questions that are currently less prominent for AAV–based gene transfer than they were 10 years ago, such as the acceptability of the risk-benefit ratio, the permissibility of trials, and the selection of participants [7,8], become relevant again.

The body of knowledge surrounding gene therapy is thus continuously evolving, and the term "gene therapy" is used to refer to several different techniques, with each having their own development trajectory from bench to bedside. This is relevant for communication about gene therapy because several authors argue that the information process surrounding gene therapy should start in childhood and continue throughout life [34,40,41]. However, it is unclear what such a process should then entail, considering that there are different techniques being developed, which all may be in a very different stage of development in several years' time. Nonetheless, it is important that the informed consent process, both in a research setting and during clinical application, incorporates the most recent insights on gene therapy, not only considering safety, effectiveness, and durability but also considering potential psychosocial impacts. Anticipating on potential psychosocial impacts might entail explicit reflection with both people with hemophilia and their relatives on what life may look like after gene transfer [51].

This review aimed to be as complete as possible in our analysis of the ethics of gene therapy for hemophilia, starting off with a systematic search and adding additional literature to that. However, because the discussion of ethical aspects is scattered throughout the literature, we may have missed some publications that are relevant to our analysis. Nonetheless, our review has highlighted ethical aspects that are relevant now that the first AAV–based gene transfer products are entering the market. Future research should monitor the psychosocial issues people with hemophilia might experience after gene therapy and focus on finding effective ways to support them, as well as find ways to communicate about novel gene therapies in an adequate manner without creating unrealistic hopes.

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AUTHOR CONTRIBUTIONS

L.B., Rvd.G., A.L.B., and K.M. designed the study. L.B. drafted the manuscript. Rvd.G., A.L.B., and K.M. critically reviewed the manuscript and provided important intellectual inputs. E.Sv.H. provided important intellectual input to the section *costs and access*. L.B. and E.Sv.H. screened the articles of the initial systematic search. All authors reviewed and approved the final version.

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SUPPLEMENTARY MATERIAL

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