FROM RESTORING CLOTTING TO RETHINKING CURE

An ethical exploration of gene therapy for hemophilia

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Van het herstellen van stolling naar het herzien van genezing

Een ethische verkenning van gentherapie voor hemofilie

(met een samenvatting in het Nederlands)

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CHAPTER 1

General introduction

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Throughout the 19th and 20th centuries, several members of European royal families died at a young age after seemingly minor incidents, such as a fall, surgery or car accident. Although these events would be non-lethal to most people, these princes and dukes all died after excessive bleeding following the incident (1). They suffered from the "royal disease", the clotting disorder hemophilia, which affected three generations of descendants of Queen Victoria of England. Through marriages between various royal houses, hemophilia was spread over the royal families of England, Germany, Russia and Spain (1). One of the best-known descendants with hemophilia – although he did not die of the consequences of hemophilia but of those of the Russian Revolution – was the last Russian Tsesarevich Alexei Nikolaevich Romanov (1). Alexei was treated by royal physician Grigori Rasputin, who was thought to possess a power of healing that could cure Alexei's hemophilia. Some of Rasputin's methods align with current medical practice, such as the importance of avoiding aspirin to prevent excessive bleeding. Some of his other strategies aimed at curing hemophilia, such as extensive prayer, sound therapy and hypnosis, are no longer considered to be treatment options for hemophilia.

Instead, in the second half of the 20th century various medications were developed that aim to restore blood clotting, thereby suppressing the symptoms of hemophilia. From the 1990s onward, progress in the field of genetics has led to the hope that, eventually, a gene therapy will provide a cure for hemophilia. Since then, several decades of research and trials followed, and in 2022 the first gene therapy product for hemophilia was approved by the European Medicines Agency and the United States Food and Drug Administration. At the same time, the development of gene therapies also raises ethical questions. For instance, due to a changing treatment landscape, it becomes unclear for people living with hemophilia and their health care providers how they should compare the risks and benefits of certain treatment options. Furthermore, although gene therapy promises a cure for hemophilia, it remains unclear what is meant with a cure. Therefore, this dissertation aims to evaluate how gene therapy can be further developed and integrated into clinical practice in an ethically responsible manner, responsive to the needs of key stakeholders.

Background

Hemophilia treatment

Hemophilia is a rare, X-linked congenital bleeding disorder caused by a mutation in the F8 gene (hemophilia A) or F9 gene (hemophilia B). As a result, people living with hemophilia have a lack of clotting factor FVIII (hemophilia A) or FIX (hemophilia B), which leads to spontaneous and trauma-induced bleeding into muscles and joints (2). Based on coagulation factor levels, hemophilia is classified into three categories of severity: mild (coagulation factor levels 5-50%), moderate (coagulation factor levels 1-5%) or severe (coagulation factor levels <1%) (2). People living with severe hemophilia use prophylactic treatment to prevent bleeding, whereas people living with moderate or mild hemophilia usually only use medication after trauma or in anticipation of a surgery (2).

Because hemophilia is an X-linked disorder, it was traditionally thought to only affect males, whereas women with a heterozygous gene variant for hemophilia were called a "carrier" (3). Recently, this nomenclature has been criticized because it does not reflect the experiences and burdens of women living with hemostatic challenges (2). Given that most standard definitions of hemophilia only include men, the prevalence of hemophilia is mainly studied in men. Research indicates that hemophilia A affects around 17 per 100.000 males (of which 6 per 100.000 severe) and hemophilia B affects 4 per 100.000 males (of which 1 per 100.000 severe) (4).

Treatment for hemophilia is aimed at restoring clotting. The palette of treatment options has grown extensively over the past decades (5,6). In the 1960s, no other treatment option than blood plasma to replace factors VIII or IX was available, as a result of which people living with hemophilia had a life expectancy of 20 to 30 years (7). The first improvement of the standard of care for hemophilia came in the 1970s, when it became possible to use freeze-dried plasma products. This allowed for home treatment, resulting in a decrease in hemorrhages and increase in life expectancy (7). However, this progress was interrupted when many people living with hemophilia became infected with hepatitis C virus (HCV) and/or human immunodeficiency virus (HIV) due to contaminated blood products in the 1980s (5). From the 1990s onward, blood-borne infections were no longer a concern, as recombinant coagulation FVIII and FIX entered the market. Since then, research has aimed at further decreasing the number of bleeding episodes and reducing the burden of treatment (5).

The availability of home treatment proved to be a great improvement in quality of life (5). Yet, the standard of care, prophylactic clotting factor replacement therapy, can be burdensome for people living with hemophilia, as the treatment requires intravenous injections two to three times a week (8). This burden is mitigated through the advent of clotting factor products with an extended half-life, decreasing the number of injections required, which reached the market in the 2010s (5).

Moreover, in 2017 the non-replacement product emicizumab became available for people with hemophilia A. An important advantage of emicizumab is that the product can be injected subcutaneously and with a lower frequency, roughly once every two weeks. Other non-replacement products for hemophilia A and B are under development (5,6). As a result of these developments, people with hemophilia in the Netherlands now have a life expectancy close to that of the general male population and have increasing levels of socioeconomic participation (9,10).

Alongside these developments, there have been high hopes for gene therapy. In the field of hemophilia, gene therapy appears to be mainly embraced for its potential to provide a cure (5,11,12). The initial progress that has been achieved has been described as "miraculous" (5). Hemophilia has long been recognized as the ideal test case for validating more general gene therapy principles, as hemophilia is a single-gene disorder with a wide therapeutic window; a minimal expression of the gene can lead to great clinical improvements; and the outcome of gene therapy (i.e. an increase is clotting factor levels) is easily measurable (2,13,14). As a result, it was once concluded that if gene therapy does not work for hemophilia, it will not work for any disorder (13).

Gene therapy definitions

The idea that intervention in patients' genetic material could provide a treatment for disease first arose half a century ago, in the 1960s and 1970s (15,16). Since then, the notion of gene therapy has sparked high expectations among both scientists and the public, as gene therapy is, at least in theory, capable of providing a durable effective treatment for various disorders with just a single intervention (17).

Defining gene therapy has shown to be challenging, and multiple definitions are currently in use. The European Medicines Agency (EMA) adheres to the following definition: "Gene therapy medicinal product means a biological medicinal product which has the following characteristics: (a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence; (b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence. Gene therapy medicinal products shall not include vaccines against infectious diseases" (18). The United States' Food and Drug Administration (FDA) adopts a wider definition: "Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use" (19). Similar definitions are provided by authors in the field, such as "[gene therapy is] the treatment of disorder or disease through transfer of engineered genetic material into human cells, often by viral transduction" (20).

These "standard" definitions have been criticized by ethicist Jonathan Kimmelman for three reasons (21). First, he argues that such techniques have been called "therapy" without any evidence of safety or efficacy. Second, he argues that these definitions are incomprehensive, because some studies falling under the category "gene therapy" actually involve "gene marking". Third, Kimmelman argues that the most controversial extensions of gene therapy concern "enhancement", for instance aimed at improving performance or towards cosmetic ends, which fall outside of the scope of the so-called "standard" definitions. Instead of these definitions, Kimmelman suggests adopting a broader definition, "the use of genetic materials, genetic-based strategies, or genetically modified organisms to study or modify human biology" (21).

Gene therapy can be directed at various ends. Whereas gene therapy development initially focused mainly on developing treatments for inherited disorders, there is now an increasing amount of research being done on gene therapy for cancers (17). In March 2023, 68% of all approved gene therapy trials was directed at developing a treatment for a cancer (22). Furthermore, it is important to distinguish between somatic and germline gene therapy. Whereas somatic gene therapy affects somatic cells of the patient being treated, germline gene therapy alters germ cells or embryo's, thereby altering the genome of future generations (23). Research on hemophilia gene therapy has thus far been directed at somatic gene therapy. Germline modification raises different ethical questions, which are not included in this thesis.

Because of the wide variety in techniques used as well as aims pursued, it has been argued that the field of gene therapy is "elastic, heterogenous and evolving" (21). In this thesis, I therefore adopt the broad definition of gene therapy proposed by Kimmelman. I will use the phrase "gene therapy" when referring to the technology in general and "gene therapies" or "gene therapy products" when referring to specific applications.

Current gene therapy techniques

There are several ways through which gene therapies can be administered to the body. The first tool that was developed, which is also the most commonly used strategy at the moment, is through recombinant viral vectors, in particular retroviruses and adeno-associated viruses (AAV) (17,21). Whereas viral vectors only allow for the addition of genes, newer genome editing techniques have, at least in theory, more potential. Such techniques are still in earlier stages of development, but are expected to be capable of targeted modifications in cells. Examples of such techniques are zinc finger nucleases (ZFNs), TALENs and, considered to be most promising and impactful for the gene therapy landscape, CRISPR-Cas9 techniques (17).

In the field of hemophilia, most progress has been made with the development

of AAV-mediated gene transfer strategies, whereby the gene coding for FVIII or FIX is inserted into an AAV-virus, which then makes its way to the liver, where the gene is used to start production of the missing clotting factor. In 2021, at the start of this PhD trajectory, no gene therapy for either hemophilia A or B had received market authorization. However, in 2022 and 2023 the first gene therapy products for hemophilia A, Roctavian (valoctocogene roxaparvovec), and hemophilia B, Hemgenix (etranacogene dezaparvovec), received market authorization by both the EMA and the FDA. A second gene therapy for hemophilia B, BEQVEZ (fidanocogene elaparvovec), received market authorization by the FDA and EMA in 2024 (24). The gene therapies currently approved are all forms of AAV-mediated gene transfer. The results of several phase 1/2 studies indicate that these gene therapies for both hemophilia A and B are capable of raising clotting factors to the mild or even normal range (14). However, there are still many uncertainties, the effects appear to decrease over time, and long-term follow-up data are still missing (14).

Other approaches to gene therapy for hemophilia are also being explored. For instance, several clinical trials for gene transfer with a lentiviral vector are being planned and conducted (25), and gene editing techniques, such as CRISPR-Cas9, are discussed in the literature (11,12,26). Recently, the first data of a phase 1 trial with gene therapy used hematopoietic stem-cells were published (27).

A history of challenges, disappointment and some progress

In spite of the high expectations that have surrounded gene therapy from the very start, authors describing the history and progress of the field generally emphasize the challenges, failures and unfulfilled promises that came along the way (13,21,28), with some describing the road towards clinical application as "long and tortuous" (17).

The best known and most infamous incident in the field concerns the so-called "biotech death" of Jesse Gelsinger (29). In September 1999, 18-year-old Jesse Gelsinger died after having participated in a phase 1 dose-escalation gene transfer trial at the University of Pennsylvania's Institute for Human Gene Therapy (IHGT). Gelsinger suffered from a mild form of ornithine transcarbamylase deficiency, a disorder leading to excessive accumulation of nitrogen in the blood. Gelsinger's mild form of the disease could be controlled with diet and drug treatment, but he wanted to participate in the trial to help newborns with a severe form of the disease, who would die as infants without a treatment (29). Investigation of the case concluded that his death, four days after insertion of the investigational therapy, had most likely resulted from an immune reaction to the adenoviral vector used (30).

The case drew attention to several shortcomings that had accumulated in both the ethical oversight and the research itself. Analyses of the case have suggested that the study protocol was violated; changes to the protocol mandated by the FDA were not implemented; adverse side effects were not reported to the FDA; Institutional

Review Board (IRBs) reviewing the protocol had acted inadequately; financial conflicts of interest may have put pressure on the principle researcher; Gelsinger's liver was not functioning at the minimum level required on the first day of the study; and Gelsinger's father argued the informed consent had been inadequate (21,29–31). When the FDA and NIH reminded researchers of their obligation to report adverse events after this incident, the NIH received almost 700 reports, including reports of multiple deaths that had occurred in gene transfer trials during the years before (30).

Over the years, gene therapy research has led to several achievements as well. The first successful applications of gene therapy came at the beginning of the current century. In 2003, the first ever gene therapy product worldwide, Gendicine, was approved in China for the treatment of head- and neck squamous cell carcinoma (28). The first gene therapy for a Western market was approved in 2012, when the EMA approved Glybera, an adeno-associated viral vector encoding the gene for lipoprotein lipase (LPL) protein (32). Successes in the field are often heralded with widespread enthusiasm in news media, a phenomenon that has been going on since the start of the Human Genome Project in the 1990s (33). For instance, Dutch media published extensively about a young child with SMA who could not sit up right at first, but learned to walk (with a walker) after being treated with the gene therapy Spinraza (34). Similarly, on several occasions, news media have described promising results from a phase 1 trial as having been curative and/or revolutionary (e.g. (35,36)).

Ethical aspects of hemophilia gene therapy

The development of new treatment options raises ethical questions as well. How should be proceed in the face of uncertainty? How can we compare the risks and benefits of several different treatment options? And what information does a patient need to make an informed choice? Ethics research can help to identify and understand such questions, thereby helping to navigate ethical dilemmas that arise. Many of the issues that have been identified and discussed in the ethics literature concern research ethical questions. For instance, an important question concerns the selection of trial participants (21,37–40). Up until the case of Gelsinger, most phase 1 gene therapy trials were conducted with volunteers with an advanced and refractory disease, as this offers the most favorable risk-benefit ratio, a method that is often adopted in trials for cancer treatments as well (21). In the trial in which Gelsinger participated, a different approach was taken. Whereas including terminally ill infants would have provided the optimal risk-benefit ratio, it was argued that a "stable volunteer" model of subject selection, in which participants are disease-afflicted but medically stable, should be adopted, because these volunteers are able to provide informed consent (21,30).

Similar questions regarding participant selection have arisen regarding gene therapy for hemophilia. In resource-rich settings, hemophilia has become a

disorder for which a good standard of care exists, as a result of which it may be hard to obtain a favorable risk-benefit ratio for trial participants. For many people with hemophilia in resource-poor settings, however, participation in a trial may be the only way to access care and treatment. This has led to debate concerning the ethical permissibility of conducting trials in resource-poor settings. Doing so may offer a more favorable risk-benefit ratio but raises concern about the vulnerable position of participants and their ability of provide informed consent, without the occurrence of therapeutic misestimation (37,39,41).

Additionally, gene therapy research has raised questions about how to assess risks and benefits in trials and how to deal with the uncertainty that surrounds translational research (21,37,42–44). It has been argued that the uncertainty in early-phase gene therapy trials is much more extensive than for other therapies under development, as it concerns an active biological agent with a complex composition, long-term impacts, immune-based toxicity and a nonlinear dose-response relationship (21). As a result, it becomes harder to assess expected risks and benefits, which also poses challenges to informed consent (37,40,44).

Furthermore, there are several elements that make gene therapy ethically distinct from other treatment options for hemophilia. First, at least with the current state-of-the-art, gene therapy cannot be repeated. This means that people with hemophilia who participate in early-phase trials will probably be excluded from potentially more effective later phase trials (45,46). Second, gene therapy cannot be undone, which means that if the gene construct is the cause of unwanted side-effects, it cannot be removed from the body (21).

Ethics research surrounding somatic gene therapy has thus mostly focused on research ethical questions. However, after several decades of research, the first gene therapy products are now reaching clinical application. As a result of this, the field is transitioning from research to care, which impacts the ethical questions that are salient. For instance, there is a more extensive knowledge base of risks and benefits, which decreases the uncertainty of current and future hemophilia gene transfer trials. At the same time, the field is continuously exploring other gene therapy techniques, raising new questions about risks and benefits. Moreover, the adoption of gene therapies in clinical care raises new ethical questions. For instance, there are concerns about the affordability and accessibility of gene therapy (46–48). Gene therapy products that have entered the market thus far belong to the most expensive drugs in the world, as a result of which they are inaccessible to many patients, including patients in resource-rich settings (49). Furthermore, new biomedical technologies such as gene therapy often change underlying concepts and definitions of disease, which may impact the desirability of the technology (50). Therefore, an analysis of implied concepts is valuable for ethical agenda setting (50).

Aim and approach of this thesis

Research aim and questions

The aim of this thesis is to evaluate how gene therapy can be further developed and integrated into clinical practice in an ethically responsible manner, responsive to the needs of key stakeholders. In order to achieve this, two main research questions are defined: 1. What are the ethical aspects of hemophilia gene therapy? And 2. What does it mean to cure hemophilia?

The first research question employs empirical methods in order to identify various ethical considerations that are relevant for gene therapy, in its current developmental phase and in the current treatment landscape. The second question is concerned with the programmatic orientation of gene therapy development, scrutinizing the concept of cure used in the field.

Approach

Ethics parallel research and patient representative participation

In order to study the research questions, this thesis employs ethics parallel research (51). Ethics parallel research aims to provide ethical guidance in early stages of technology development and to provide input for the normative reflection on these technologies (51). This goal can be achieved through the combination of six related and sometimes overlapping elements: disentangling wicked problems, upstream and midstream ethical analysis, ethics from within, inclusion of empirical research, public participation and mapping both hard and soft societal impacts (51).

Conducting research in this way requires inter- and transdisciplinary collaboration with other researchers as well as other experts and stakeholders in the field. To achieve this, this PhD research was conducted as part of the larger SYMPHONY consortium, in which physicians, fundamental researchers, social scientists, ethicists, and representatives from the Dutch association for everyone with a heritable clotting disorder (NVHP) work together with the aim of developing treatments for people with congenital bleeding disorders (52). Although no gene therapy for hemophilia is developed within this consortium, all physician-researchers who have conducted hemophilia gene therapy trials in the Netherlands were affiliated with the consortium.

The work package in which this PhD study was conducted consisted of ethicists, a hematologist and a patient representative. The studies in each of the chapters are conducted by an interdisciplinary research team, combining ethical and hematological expertise with experiential knowledge. In chapters 3 and 4, we employ active patient representative participation, whereby the representative was involved as a partner in all phases of the study, from the design of the study to publication of the paper (53). In addition, the topic list of the interview study (chapter 3) was adapted based on feedback from multiple patient representatives involved in the SYMPHONY consortium.

Empirical and normative methods

This thesis combines empirical and normative methods. Empirical ethics approaches allow to gain insight into current practices as well as stakeholders' perspectives and opinions on the matter at hand. Thereby, empirical approaches contribute to a better understanding of the problem, incorporating the unique perspective of the end-users of gene therapy, and provide input for the normative evaluations. I take a consultative approach towards the empirical findings (54).

Several methods were used in this thesis. We conducted a narrative review of the literature to identify and synthesize ethical aspects that were mentioned in the literature, thereby providing a broad overview of the research topic (55). Further, we conducted a qualitative interview study aimed at identifying stakeholders' views on ethical aspects of hemophilia gene therapy. Qualitative interviews are a useful method to identify and better understand various perspectives, thereby allowing for a better understanding of the ethical problem (56). In addition, we conducted a conceptual analysis and evaluation of the concept of 'cure'. Together, these sources form the basis for normative reflection in the General Discussion.

Outline of the thesis

The first two chapters following this introduction focus on exploring ethically relevant aspects of hemophilia gene therapy. In chapter 2, we conduct a narrative review of the literature in order to identify ethically relevant aspects, including ethical questions surrounding gene therapy development in general. Then in chapter 3, we present a qualitative interview study with stakeholders, with the aim of identifying stakeholders' morally reasoned opinions on gene therapy for hemophilia. Based on these interviews, we identify three ethical themes. We take a broader view on hemophilia care in chapter 4, where we evaluate if and how personal health records contribute to increased self-management and empowerment of people living with hemophilia. In chapters 5 and 6 we take a closer look at gene therapy's main promise, to cure hemophilia. The chapter 5 identifies three distinct interpretations of cure used in other medical fields, and evaluates which of these interpretations is most suitable in various contexts in which a cure through gene therapy is discussed. Chapter 6 presents a review of the use of cure specifically in the context of hemophilia, and relates this to discussions surrounding classification of hemophilia and concepts of disease. In the General Discussion, chapter 7, I answer the main research questions and provide recommendations for the further development and implementation of hemophilia gene therapy.

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CHAPTER 2

The ethics of gene therapy for hemophilia: a narrative review

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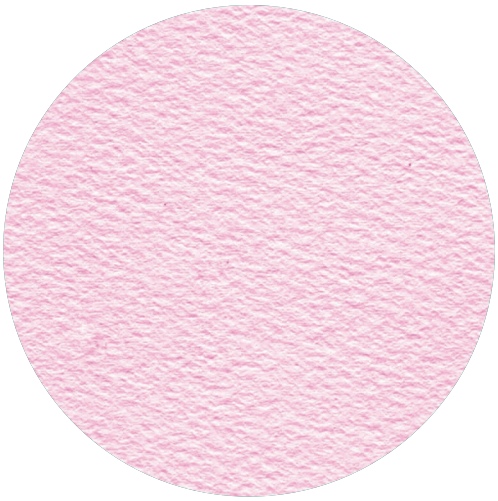
Designed chapter with co-authors; conducted the literature search, selection and analysis. Drafted the manuscript and revised based on comments from co-authors.



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 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 three 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 living 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 many treatments that temporarily relieve symptoms, and that there is a need to re-evaluate the desirability of gene therapy for hemophilia, given the availability of other treatments.

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 testcase for validating gene therapy principles, as it is a monogenic disorder with a wide therapeutic window and its effect, i.e., 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 Union1[1]. The product is a form of AAV-mediated gene transfer; a technique in which a substitute copy of the gene coding for the missing clotting factor is delivered to the liver by means of a recombinant non-integrating AAV-vector, with the intention of achieving sustained clotting factor levels in the normal range (3). 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 offers a potential for improved treatment but also raises ethical issues. A distinctive characteristic of gene therapy trials compared to other types of trials is the high level of complexity and uncertainty (4). Furthermore, as gene therapy using an AAV-vector cannot be repeated, people who participate in early-phase trials will likely not be eligible to receive a later more effective gene therapy (5). 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 (6,7). 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 early phase trials and towards clinical application. This new phase has its own ethical aspects. For instance, introduction to the market may create challenges surrounding access and reimbursement, like many expensive treatments do (8).

As these new developments have ethical relevance, we conducted a review to take stock of the current ethical aspects of hemophilia gene therapy. Gaining insight 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 (9).

Current hemophilia treatments

Hemophilia is an X-linked congenital bleeding disorder. Due to a lack of clotting factor VIII (hemophilia A) or factor IX (hemophilia B), persons affected with a

[1] https://investors.biomarin.com/2022-08-24-First-Gene-Therapy-for-Adults-with-Severe-Hemophilia-A,-BioMarins-ROCTAVIAN-TM-valoctocogene-roxaparvovec-,-Approved-by-European-Commission-EC

severe form of hemophilia suffer from spontaneous and trauma-induced bleeding into muscles and joints, resulting in chronic pain and loss of function (3,10). Severe hemophilia affects around 1 in 10.000 males worldwide (11).

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 living 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 living with hemophilia worldwide do not have access to adequate care (12). 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 (13), and emicizumab for hemophilia A, a non-replacement therapy, which requires lower frequency and subcutaneous instead of intravenous injections (14).

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, as 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, since 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 supplementary file.

Ethical themes

Based on our analysis of the literature, we constructed three 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.

Living up to expectations

Many authors, particularly those writing in the early 2000s, express the hope that gene therapy will eventually cure hemophilia (15–20). 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, the high costs, inhibitor development and the difficulty of venous access in small children (6,21).

Recent research indicates that AAV-based gene transfer therapies can indeed raise FVIII and FIX levels to a normal range, with effects lasting several years (22,23). 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 (23). 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 (23,24).

Furthermore, there are several groups of persons living with hemophilia for whom gene therapies currently being tested are likely ineffective. The current products are not suitable for children living with hemophilia, and probably ineffective for people with inhibitors, as a result of which they are excluded from most trials (23,24). Also excluded from trials with the current liver-directed products are people with liver disease, which is prevalent in the hemophilia population because of historic exposure to HCV-infected blood products. In addition, gene therapies using 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 (25). Furthermore, as other novel therapies have improved the standard of care for hemophilia during the last few years, some expect that many patients will prefer these other treatment options over gene therapy (26). These challenges have been described as discrepancies between hopes and reality of gene therapy for people living with hemophilia (27).

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 people living with hemophilia and physicians. Whereas 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 (23). Similarly, several authors express the hope that gene therapy will become available for people living with moderate hemophilia, a group that does mostly not experience spontaneous bleedings and would therefore only benefit from higher factor levels (27,28).

Furthermore, there are new insights regarding 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 (7,21,29–31). The most serious concern based on recent data appears to be rising liver transaminases, for which patients require immunosuppressive therapy (22,23,32). 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 (22). 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 (33). Furthermore, several groups of authors warn that contrary to what is generally believed, AAV vectors do sometimes integrate (13,32,34). 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 (32).

Simultaneously, it is clear from the literature that there is hope that other forms of gene therapy will be more effective, such as gene transfer using a lentiviral vector or lipid nanoparticles, gene therapies through stem cell therapy or gene editing technologies. However, these techniques are still in earlier, mainly preclinical, stages of development than AAV-based gene transfer (14,35).

The updated insights on 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 potential participants have about the nature and aims of gene therapy trials (6,7,36–38). 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 (33). Fully understanding the goals of gene therapy as well as the risks and uncertainties surrounding it is considered particularly important because once administered, the vector with the gene therapy product cannot be discontinued (33,39). To tackle these difficulties in informed consent, some argue that the information process about gene therapy should begin in childhood and continue throughout life, in order to facilitate a well-informed decision (33,40).

Psychosocial impacts

Some empirical articles describe concerns by people living with hemophilia about the impact of gene therapy on their identity. Some people living 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 not to want gene therapy (41,42). Fletcher et al. hypothesize that this loss of identity feared by people living with hemophilia may be the result of the loss of the diagnosis of hemophilia, and refer to literature describing the "burden of normality". The burden of normality has mainly been described for Deep Brain Stimulation as treatment for epilepsy or Parkinson's disease. It describes the phenomenon of patients having to adjust to a symptom-free life after their treatment (43). In these cases, the burden of normality does not result from side-effects of psychosurgery, such as mood disturbances, but from the psychological experience of becoming symptom-free (43,44).

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 (45,46). As hemophilia is a congenital disorder that has a large impact on affected persons' lives (47,48), 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 (49).

In all these examples, the threat to personal identity is described as the result of a "biographical disruption", in which people cannot integrate an event into the personal story they tell about themselves (45). Personal identity is thus conceptualized in a narrative sense, which defines identity as "selfhood […] essentially tied not directly to defining traits, but to our ability to understand ourselves and others in narrative terms" (50, 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 identity can be threatened if these core characteristics are affected (50). 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 (43,50,51).

To our knowledge, there are no reports of people living with hemophilia who experienced a change in their identity after participating in a gene therapy trial. Therefore, it remains uncertain if and how a change in identity will be experienced in practice, in particular because gene therapy may only provide a temporary rather than a life-long "cure". However, it has been described that difficulty with psychological adjustment can occur both in the short-term and in the long-term after treatment (50), which gives reason to not exclude the possibility of similar experiences for people living with hemophilia, even if gene therapy only works temporarily.

At the same time, there are reports of trial participants who wished there had been more attention for psychosocial aspects throughout the process and patients who felt they lost control over their situation as a result of trial procedures (33). Furthermore, some trial participants expressed experiencing anxiety about the uncertainty concerning the duration of the effects and said psychological support might be required when the effects decrease (33). In addition, several authors argue for the importance of providing psychosocial support to people living with

hemophilia receiving gene therapy in a trial or as a treatment (12,28,32).

A potential change in identity has several ethical consequences. Most importantly, the burden of normality changes the risk-benefit ratio of a treatment, as such changes in identity may be undesirable to patients (43). In order 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 (43,50). 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 (12).

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 (8). 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 treatment (52–54). 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 (52,54). Calculations of cost-effectiveness are also hampered by opacity about the actual price that is paid for current prophylactic treatment (52). 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 (21,32,36,55).

The high costs in combination with remaining uncertainty regarding cost-effectiveness creates considerable risks for healthcare 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 (56,57). In discussions on the payment for such novel therapies, it is important to consider that in resource-rich settings, hemophilia is no longer a life-threatening illness. For instance, with currently available treatments, people living with hemophilia in the Netherlands have a life expectancy that is close to that of the general male population (58).

Payment for the development or reimbursement for the use of expensive medications for rare diseases raises an ethical dilemma. On the 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 (59). In most ethical discussions surrounding the dilemma of allocating scarce resources for rare diseases, the principle of non-abandonment or the rule-of-rescue, which is an imperative to save people who are in immediate danger, are invoked because there is no treatment available for many of these rare diseases, creating a large unmet need for the affected patients (59,60). 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 (60). However, as there are currently alternative treatments available for hemophilia and further treatments are being developed, the principle of non-abandonment and the rule-of-rescue lose some moral weight.

In contrast, it is estimated that around 75% of people living 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 (19,26). The World Federation of Hemophilia has also embraced gene therapy as a potential source for achieving its goal of "treatment for all" (12). 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. Further, 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 (27). As a result, there is a risk that gene therapy widens the treatment gap between high-resource and low-resource settings.

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 effects appear to decrease over time • Gene therapy is unsuitable for children, people with inhibitors, people with liver damage and people with pre-existing antibodies • The improved standard of care for hemophilia has heightened expectations of gene therapy • There are risks of side-effects which may require treatment with immunosuppressive therapy • The informed consent process should be elaborate in a treatment setting as well, because of 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 • Decreasing 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 non-abandonment has less moral weight • The expected costs may widen the treatment gap between low-resource and high-resource settings

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, as people would need support dealing with that uncertainty, as well as in the scenario where gene therapy turns out to be a cure, as people would have to adjust to a life without the symptoms of hemophilia. Last, 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 living with hemophilia in low-resource settings who currently do not have access to treatment.

These insights call for a re-evaluation 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 (29). 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 (3,14). As a result, gene therapy may be more valuable for some people living with hemophilia than for others.

Further, 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", after only having data of 10 participants up to 26 weeks after gene transfer (61). Instead, it appears as though gene therapy will become one among several treatments available for hemophilia which relieve 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 (7) 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. As 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 ten years ago, such as the acceptability of the risk-benefit ratio, the permissibility of trials and the selection of participants (6,7) 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, which each have their own development trajectory from bench to bedside. This is relevant for communication about gene therapy, as several authors argue that the information process surrounding gene therapy should start in childhood and continue throughout life (33,39,40). 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 as well as 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 living with hemophilia and their relatives on what life may look like after gene transfer (50).

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, as 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 living 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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Supplementary file: Search strings

Embase:
('Plasma Thromboplastin Component Deficien*':ti,ab,kw OR 'ptc deficien*':ti,ab,kw OR 'factor ix deficien*':ti,ab,kw OR 'factor 9 deficien*':ti,ab,kw OR 'f9 deficien*':ti,ab,kw OR 'fix deficien*':ti,ab,kw OR 'hemophilia B'/exp OR Hemophilia:ti,ab,kw OR Haemophilia:ti,ab,kw OR 'factor VIII deficien*':ti,ab,kw OR 'factor 8 deficien*':ti,ab,kw OR 'Hemophilia A'/exp OR 'f8 deficien*':ti,ab,kw OR 'fviii deficien*':ti,ab,kw) AND ('moral*':ti,ab,kw OR 'ethic*':ti,ab,kw OR 'bioethic*':ti,ab,kw OR 'desirab*':ti,ab,kw OR 'acceptab*':ti,ab,kw OR 'patient perspective*':ti,ab,kw OR 'patients perspective*':ti,ab,kw OR 'parent perspective*':ti,ab,kw OR 'parental perspective*':ti,ab,kw OR 'ethics'/exp) AND ('gene therap*':ti,ab,kw OR 'genetic therap*':ti,ab,kw OR 'DNA therap*':ti,ab,kw OR 'gene transfer*':ti,ab,kw OR 'base edit*':ti,ab,kw OR 'prime editing':ti,ab,kw OR 'genetic transfer':ti,ab,kw OR 'gene therapy'/exp OR 'gene transfer'/de)

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Web of Science:
TS=("plasma thromboplastin component deficien*" OR "ptc deficien*" OR "factor ix deficien*" OR " factor 9 deficien*" OR " f9 deficien*" OR "fix deficien*" OR "haemophilia" OR "hemophilia" OR "factor VIII deficien*" OR "factor 8 deficien*" OR " f8 deficien*" OR " fviii deficien*") AND TS=(moral* OR ethic* OR bioethic* OR desirab* OR acceptab* OR "patient perspective*" OR "patients perspective*" OR "parent perspective*" OR "parental perspective*") AND TS=("gene therap*" OR "genetic therap*" OR "DNA therap*" OR " gene transfer*" OR " genetic transfer*" OR " base edit*" OR " prime edit*")

CHAPTER 3

Ethical aspects of hemophilia gene therapy: a qualitative interview study with stakeholders

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Contribution of the author of this dissertation:
Designed chapter with co-authors; conducted the interviews and analysis. Drafted the manuscript and revised based on comments from co-authors.

Abstract

Background: There are great expectations for the potential role of gene therapy in the treatment of hemophilia. At the same time, developments in the field of hemophilia gene therapy have always raised ethical issues. It remains unknown how these ethical issues are perceived by stakeholders, particularly regarding the most recent developments in the field.

Objectives: To obtain insight into stakeholders' morally reasoned opinions on gene therapy for hemophilia.

Methods: We conducted qualitative research with Dutch people living with hemophilia (n=13), parents of children living with hemophilia (n=5), physicians (n=4), nurses (n=3), a regulator (n=1) and a representative from a pharmaceutical company (n=1). We conducted semi-structured interviews based on a topic list and reported the results according to the COREQ guidelines.

Results: We identified three main themes. The theme freedom and independence describes the hope people living with hemophilia have of increasing their freedom through gene therapy, as well as concerns that gene therapy increases their dependence on their treatment center. The theme trust and altruism describes how people living with hemophilia have a high level of trust in their physician and treatment center as well as in scientific research. As a result of this trust, they are willing to participate in research to help other people living with hemophilia. The theme incremental benefits describes doubts respondents have about the added value of gene therapy compared to standard treatment.

Conclusions: Stakeholders embrace the theoretical potential of gene therapy, while several people living with hemophilia question the added value of AAV-mediated gene transfer products for themselves.

Introduction

Since research on hemophilia gene therapy started, there have been great expectations of its potential for the treatment of hemophilia. If left untreated, the lack of clotting factor VIII (hemophilia A) or factor IX (hemophilia B) leads to spontaneous and trauma-induced bleeding into muscles and joints. As a result, people living with hemophilia suffer from chronic pain and loss of function (1,2). Currently, several treatment options are available, with several advantages and drawbacks. Prophylactic clotting factor replacement therapy prevents bleeds for most people living with hemophilia. However, the intravenous injections are experienced as burdensome and the product is expensive. The burden of the injections has been mitigated by the recent introduction of extended half-life products which lower the frequency of intravenous injections, and the non-replacement therapy emicizumab which requires subcutaneous instead of intravenous injections (1,3,4). However, as these options still require regular injections and offer no prospect of a cure, there are great expectations for gene therapy. In 2022, the first gene therapy products for hemophilia A and B received conditional market authorization (5,6).

Throughout its development, gene therapy has raised ethical concerns. When the first clinical trials were starting, the high levels of uncertainty surrounding these trials raised concerns about the acceptability of the risks imposed by these studies and raised questions about which patients to include (7,8). Recently, ethical concerns have been identified concerning whether gene therapy can fulfill the (great) expectations, its impact on psychosocial aspects and its high costs (9).

As hemophilia gene therapy research continues and the technique is further developed, expectations of what gene therapy could achieve are increasing (10). However, it is unknown what stakeholders of hemophilia gene therapy hope to achieve with gene therapy and how the ongoing progress in the field affects their views on the desirability of gene therapy. Therefore, we conducted a qualitative interview study to identify stakeholders' morally reasoned opinions on the ethics of gene therapy for hemophilia.

Methods

Qualitative interviews are a valuable method to identify and better understand perspectives. Thereby, interviews can improve our understanding of ethical implications of gene therapy (11). To validate our findings, we conducted an expert meeting after roughly two-thirds of the interviews had been conducted (12). The study is reported in accordance with the consolidated criteria for reporting qualitative research (COREQ) (13).

Participant selection and recruitment

We included a wide variety of Dutch stakeholders. As the goal of this qualitative

study was not to compare the perspectives of different groups of stakeholders, but to obtain an overview of the scope of perspectives and opinions regarding ethical aspects of hemophilia gene therapy, we made use of purposive sampling (14). Purposive sampling allows to make sure that specific types of cases become part of the final sample (14). We used this strategy to include participants from a variety of backgrounds, thereby allowing for a broad range of perspectives. As part of this range of perspectives, we also included people who were cured from hemophilia through a liver transplantation, as they have a unique experience of first living with hemophilia and later living without hemophilia. This group was included as one of the promises of gene therapy is that it will provide a definitive cure, irrespective of whether current gene therapies can deliver on this promise. Because gene therapy is currently only under development for severe hemophilia, we did not include (parents of) people with mild or moderate hemophilia.

In total, we conducted 27 interviews with people living with hemophilia who participated in a gene therapy trial (n=4), people living with hemophilia who underwent a liver transplantation (n=3), other people living with hemophilia (n=6), parents of children living with hemophilia (n=5), physicians (n=4), nurses (n=3), an employee from a pharmaceutical company (n=1) and a regulator (n=1). One of the included physicians and one of the included nurses were specialized in hemophilia care for children, the others in hemophilia care for adults. We included participants affiliated with all six hemophilia treatment centers in the Netherlands. Characteristics of the respondents can be found in table 1.

Potential participants were approached in various ways. We targeted people living with hemophilia and parents of children living with hemophilia through an advertisement in the newsletter and social media of the Dutch association for everyone with a congenital clotting disorder (NVHP), as well as through their health care providers. Most professionals were invited directly by one of the authors (LB or KM) and nurses were also invited during a meeting of the nurses' society. Furthermore, both people living with hemophilia and professionals were recruited through word of mouth. Recruitment was completed when saturation was reached regarding codes and meaning (15).

Before the interview, LB sent participants an e-mail containing the information letter and consent form. Additionally, she had a telephone call with all people living with hemophilia and parents before the interview. LB had already met some of the professionals prior to inviting them for an interview. Participants were informed that the aim of the study was to identify ethical aspects of gene therapy for hemophilia and that the study was part of the SYMPHONY consortium (16). Participants who asked about the background of the interviewer were informed that LB (MSc MA) does not have a medical background, is trained in bioethics, and that this study is part of her PhD research.

One invited physician declined participation because they considered themselves not knowledgeable enough. Two people who are active in the patient community and who responded to the advertisement were invited to participate in the validation meeting instead, because there were already several respondents with similar characteristics. Three physicians who were invited to participate in the validation meeting declined as they could not make the scheduled timeslot. Staff members of one treatment center were unwilling to invite their patients because they wanted to avoid overloading their patients with research participation requests.

Table 1: Respondent characteristics

Role	N
Person with hemophilia A (no gene therapy trial participation)	6
Person with hemophilia B (no gene therapy trial participation)	-
Parent of child with hemophilia A	4
Parent of child with hemophilia B	1
Trial participant with hemophilia A	1
Trial participant with hemophilia B	3
Person who no longer has hemophilia after liver transplantation	3
Physician (involved in gene therapy trial)	2
Physician (not involved in gene therapy trial)	2
Nurse (involved in gene therapy trial)	1
Nurse (not involved in gene therapy trial)	2
Regulator	1
Employee pharmaceutical company	1

Data collection

Semi-structured interviews based on a topic list were conducted by LB. The topic list was designed based on experiential knowledge of the research team and a literature study conducted by part of the research team (9). The list was continuously evaluated and adapted as the interviews progressed, to allow for the inclusion of new topics in further interviews. Although several participants brought up the costs of gene therapy, we did not include this as a topic, because the costs of gene therapy were unknown at the time of the study.

The interviews were conducted face-to-face at the participant's home or workplace, in a public place, or digitally via Microsoft Teams, depending on COVID-19 restrictions and the participant's preferences. The interviews were audio-recorded, transcribed verbatim and pseudonymized. After the interview, LB took notes of impressions of the interview and relevant remarks made by the participant before or after the audio-recorder was switched on.

During most interviews only the interviewer and participant were present. In some cases, a partner or child of the participant was in the room. Some interviews

were briefly disrupted by another person, infant or pet. During one digital interview with a person living with hemophilia, colleagues of the participant were present in the background. As this participant was active in the patient community and frequently spoke in public about their experience of living with hemophilia, we do not expect that this impacted their responses. The interviews lasted between 30 and 108 minutes, with a median duration of 49 minutes.

Data analysis

The pseudonymized transcripts were analyzed thematically (17). An initial list of codes was developed based on the topic list, familiarization with the data and discussion within the research team. All interviews were coded by LB with NVivo 12 software. Ten interviews were double coded by an intern, after which the codes were compared and discussed to assert inter-coder reliability (17). The process started with open coding, during which memos were made. The developed codes and memos served as the basis for developing higher-order codes and themes in discussion with the entire research team. The meaning of individual text fragments was determined by interpreting them in the context of the entire interview. During the analysis, codes were constantly evaluated and adapted, and new codes were developed if necessary. We went back and forth between the different analysis steps to allow for constant comparison (18). The analysis ultimately resulted in the development of interpretive higher-order themes.

As a member check, we conducted an expert meeting after 16 interviews to discuss the accuracy and interpretation of our results (12). Participants in the expert meeting were people living with hemophilia who are involved in the NVHP (n=3), physicians (n=3) and nurses (n=2) affiliated with different hemophilia treatment centers.

Results

Our analysis identified three ethical themes: freedom and independence; trust and altruism; and incremental benefits. Each will be described in more detail below and will be illustrated with quotes from the interviews. Additional quotes belonging to each of the themes can be found in Table 2.

Theme 1: freedom and independence

Hopes of gene therapy

Respondents hoped that gene therapy, or treatment for hemophilia more generally, could offer people living with hemophilia the opportunity to live a more "normal", carefree, and independent life. For many, this meant a life unrestricted by hemophilia.

Respondents described several hindrances that people living with hemophilia encounter in daily life. As a result of their hemophilia, several respondents were not

able to choose the career or hobby they had desired. Instead, they had to be careful with physical activities. Most professionals and people living with hemophilia mentioned that these hindrances were more severe for older people who did not receive prophylactic treatment in the past than for people who have grown up with treatment available. Many of the interviewed people living with hemophilia expected that gene therapy will provide a sustained increase in clotting factor levels and thereby the certainty that they can undertake a wider range of physical activities without risking bleeds. Several respondents thought that this increase in clotting factor levels would lead to a decreased experience of pain and stiffness in joints that have been injured by previous bleeds.

Furthermore, the respondents described several hindrances that people living with hemophilia encounter resulting from their prophylactic treatment. Some indicated that the regular injections were a constant reminder of their hemophilia, and expressed the hope that gene therapy would help them to think about their disease less frequently. Some respondents also indicated that they cannot structure their day as they wish, because of the need to schedule time for administering their prophylaxis. Several individuals mentioned difficulties when traveling: having to bring medication on a holiday and having to choose holiday destinations in relative proximity to a treatment center, which made them feel restricted in their ability to travel abroad:

> *"When you're traveling, you have to bring your medication. And you have to prepare and you're not free. You are never free. And that is…. I don't want to say you're a prisoner, but you are a prisoner of the system" – R13*

Furthermore, several respondents thought that gene therapy would facilitate handling other medical conditions or treatments. For example, some described experiences with health care providers who knew too little of hemophilia to provide proper care and expressed the hope that gene therapy will simplify a visit to the dentist or undergoing other medical procedures. Further, some respondents feared that when growing old, people living with hemophilia might lose the ability to inject themselves with clotting factor, thereby becoming dependent on family members or nursing home staff, who might lack the necessary skills or time.

Limits to independence

Although several respondents provided accounts of increased independence after gene therapy, either based on their own experiences or that of their patients, there were also several people living with hemophilia who were concerned that the current results of gene therapy would make them more dependent on their treatment center. They expected gene therapy to only raise their factor levels to the range of

mild hemophilia. They reasoned that with such results they would still need clotting factor replacement in case of an injury, while people with mild hemophilia are not allowed to have a supply of clotting factor at home:

> *"The advantage of severe hemophilia compared to mild hemophilia is that we are allowed to have medicine in stock. People with mild hemophilia are not allowed to [have their own stock]. That is a handicap. Whenever you go on a holiday, you have to request extra medicine or find out if it is available abroad. I am not dependent on that; I always have it with me." – R15*

Moreover, several physicians and nurses expressed the concern that people would become less aware of their hemophilia or consider themselves hemophilia-free after gene therapy. They provided several anecdotes of people who took more risks after a gene therapy trial, in a way that was, in their view, irresponsible. Several of them said that the behavior by people who changed from severe to mild hemophilia was similar to the conduct of people who have always had mild hemophilia. The risks that people took included both physical activities that could elicit a bleed, such as heavy gardening or sports, as well as not taking proper action when a bleeding occurred:

> *"The biggest issue with people with mild hemophilia is that they call too late in case of a bleed. And now you're making these people a mild patient." – R14*

Becoming hemophilia-free and impacts on identity

Some respondents who had not received gene therapy hypothesized that they would need time to adjust to being hemophilia-free if they would ever choose it as a treatment. They thought it might feel "strange" to not rely on clotting factor injections anymore and to have fewer restraints in their lives. People who participated in a trial or received a liver transplantation also described an initial feeling of disbelief after not requiring clotting factor injections anymore. Nevertheless, all people we spoke to thought that becoming hemophilia-free was desirable.

We found no univocal indications that becoming hemophilia-free impacts a person's identity. Some healthcare providers knew a patient who explicitly stated that after gene therapy he no longer felt as a patient, which they described as a change in identity. None of the trial participants and people who underwent a liver transplantation experienced a change in their identity after "losing" hemophilia. One respondent said that he used to be chair of the patient society but had to give this up after his liver transplantation because he was no longer a person living with hemophilia after this procedure. Later, he characterized this remark as a joke and said that the decision to step down from this position fitted with his phase in life, which was retirement.

Many people living with hemophilia said that they had never let hemophilia define them and that they still tried to do as many things as possible, despite having to take their hemophilia into account. In contrast, one person mentioned that he felt his hemophilia had prevented him from developing his masculinity, as he always had to be careful, and one nurse described some of their patients as "being their hemophilia". Nonetheless, the people who described they never let their hemophilia define them spoke of the friendships they gained through the patient society and how their medical care could be a social activity. Additionally, they showed pride in their ability to inject themselves intravenously:

> *"Since I was twelve, I inject myself. I can do it while drunk. I can do it on a ship. I can do it in a moving car." – R7*

Theme 2: Trust and altruism

Trust in research

From the interviews it became clear that respondents embrace the promises of gene therapy and trust the outcomes of research. Both people living with hemophilia and health care professionals expressed that they were amazed by the potential of gene therapy and considered its goals admirable:

> *"It is incredibly wonderful that these developments are here and that patients can be helped by […] such a miracle. It is obviously incredibly impressive that people can study for so long and learn that these things can be solved" – R20*

Several respondents looked back on the advances that have been made in the treatment of hemophilia during the last decades and considered this progress an example of what science can achieve. Based on this progress, several respondents were certain that treatment options for hemophilia would continue to improve.

Moreover, some people living with hemophilia explicitly indicated that they had a lot of knowledge about how clinical trials were conducted and said that they knew this was always done correctly. Many respondents reported that they were generally trusting of science, often contrasting themselves with people who oppose COVID-19 vaccinations.

Trust in physician and treatment center

Both health care professionals and people living with hemophilia mentioned that people living with hemophilia have a lot of trust in their physician and their treatment center:

"A hemophilia patient, because it is a disease from cradle to grave, has a very important relationship with his treatment center, with his physician." – R24

Many respondents considered this trusting relationship to be very valuable, and a good starting point for discussing gene therapy. Several persons thought it is valuable that the regular treating physician can also be the person conducting the recruitment and informed consent process in a gene therapy trial. Parents and people living with hemophilia argued that they would prefer to be informed about trials by their own physician, because they knew their physician would offer them the best possible care. Several respondents also emphasized the importance of this relationship when making a shared decision on gene therapy as a treatment.

In contrast, some respondents were concerned that people living with hemophilia might too readily trust and believe their physician and would not think critically when deciding to participate in a trial, simply because it was proposed by their physician. Several physicians feel a large responsibility because of the trust placed in them, which could sometimes feel like a burden.

Altruism

Many respondents considered it important to participate in research because they had high hopes for the outcomes. Several of them also mentioned that this was a reason to participate in this interview study. Multiple trial participants also indicated that a reason to participate in a gene therapy trial was to advance science and help other people living with hemophilia, expressing the hope that younger generations would have an easier life than they had themselves. One respondent also reflected on the value that the development of gene therapy for hemophilia may have for patients with other congenital disorders. Many respondents recognized that the current standard of care could not have been achieved without the participation of other people living with hemophilia in trials.

Theme 3: Incremental benefits

Comparison with standard of care

Although respondents embrace the potential of gene therapy, several people articulated that the current results of gene therapy were not what they hoped they would be. It was often mentioned that the standard of care is already good and that it is questionable whether gene therapy can trump this, given its risks and uncertainties. Several people living with hemophilia and parents thought that gene therapy might be more valuable for others than for themselves or their child, such as either older, younger, or more physically active people.

Simultaneously, several respondents were concerned that people living with hemophilia could not always distinguish between the promises of gene therapy in

general, and the possibilities of the products that are currently being tested in trials or will be on the market soon:

> *"What strikes me most is that when you approach persons with hemophilia to ask them to participate in [gene therapy] trials, you are mainly busy tempering their expectations" – R23*

Several respondents thought that the choice for gene therapy or another treatment would depend on individual preferences. Some considered that even if gene therapy becomes an approved treatment, it may not be desirable for every person living with hemophilia. One nurse explicitly stated that she thought that gene therapy might not be suitable for everyone, depending on their personal situation. It was also argued that gene therapy might be less desirable for people living with hemophilia A than for people living with hemophilia B, as the introduction of emicizumab has improved the standard of care for hemophilia A, and the results of trials for hemophilia A are regarded as less positive than the results of trials for hemophilia B.

Many respondents explained that they themselves or their patients were thinking about the optimal timing for gene therapy. Some respondents were convinced that more effective forms of gene therapy will become available, and therefore preferred to wait for a variant that may benefit them more.

Coping with declining effects

Several respondents suggested that people should receive psychosocial support throughout and after the process of gene therapy. They argued that this would be required to help people adjust to their hemophilia-free life, but also to help them cope in case the effects of gene therapy decline and they have to use prophylaxis again. One of the trial participants also described that he had experienced a decline in the effects of gene therapy, which was an unexpected worry for him.

Fair distribution

Some respondents were concerned that when gene therapy reaches the market, there will be a higher demand than can be afforded. Therefore, they considered which patients would benefit the most. All respondents who discussed this topic argued that people living with hemophilia who have breakthrough bleeds while using prophylaxis or who had difficulties with injections would benefit most from gene therapy. Respondents disagreed about whether nonadherence to prophylaxis would be a fair criterion. Some physicians argued that they would like for a central body to decide on how gene therapy should be distributed, thereby taking away the decision from physicians and treatment centers.

Table 2: Illustrative quotes

Theme	Quote
Theme 1: Freedom and independence	
Hopes of gene therapy	"My own expectation is that gene therapy is going to normalize the life of a hemophilia patient. So, giving you a treatment that lasts a long time and that results in a constant factor 8 level, as a result of which you can just live a normal life" – R10
Limits to increased independence	"If you only inject yourself in special situations, for instance once a year, then you will lose that skill. And then the hospital will say: 'we're not letting you do this anymore'. And the hospital is probably inclined to say: 'for that one time a year, we rather have you come here instead of fumbling on your own'. And that is a situation in which a lot of people will feel like they're losing control" – R14
Becoming hemophilia-free and identity	"In the beginning [after the trial], I thought 'it is Monday, I have to inject'. But no, I did not have to inject. And on Thursday morning I had the urge to collect all items to inject myself. But no, that was not necessary anymore. In the beginning that was a very strange experience of course. You have to get used to that" – R2
Theme 2: Trust and altruism	
Trust in research	"I have a lot of trust in the sense that I think that much progress can be achieved in the next few years in the development of new medication and treatments" – R17
Trust in physician and treatment center	"Some people are really trusting of their physician who says 'Let's do this [enroll in a trial], this might be something for you'. And then they say: 'Sure, why not?'" – R12
Altruism	"When they called me to ask to participate in this study, I thought I'll just participate. If I can assist in the further development of treatments for a person with hemophilia, I'll do that" – R1
Theme 3: Incremental benefits	
Comparison with standard of care	"If you have to inject 180 times a year, then it really is an advantage if you get gene therapy and you don't have to do that anymore. But if you have emicizumab, of which the burden for the patient really is a lot smaller, then this balance [between advantages and disadvantages] will be different" – R5

Coping with declining effects	"The factor levels keep decreasing. There is going to be a moment, I don't know if it will be a year or two years or ten years, but there is going to be a moment in which I have to inject prophylaxis again. […] In the beginning, whenever I did a blood test, I immediately went to the website to check the results. And now I stopped doing that, because I noticed every time my factor levels went down I thought 'shit' […] and I started thinking about it a lot" – R20
Fair distribution	"I think the biggest ethical challenge will be how we are going to distribute this over the patients, because this is never going to be reimbursed for the entire population" – R4

Discussion

This study provides insight into stakeholders' morally reasoned opinions on several ethical aspects of gene therapy for hemophilia. Based on our analysis we identified three main ethical themes: freedom and independence; trust and altruism; and incremental benefits. In the following section, we will relate our findings to broader discussions in the literature and highlight topics that are underexplored. Finally, we will list this study's strengths and limitations and provide recommendations for further research.

Discrepancy between wishes and reality

Our results indicate that stakeholders have several hopes for gene therapy that may be unachievable. People living with hemophilia hope to increase their freedom, but many fear that they will become more dependent after gene therapy. Many respondents hope that they will be able to forget about their hemophilia after gene therapy, but healthcare providers are concerned about the potential consequences when people pay insufficient attention to their hemophilia. Lastly, many people admire the overall goals of gene therapy, but question the added value of gene therapy products that are currently in advanced stages of development.

A literature study previously conducted by a part of our research team already raised questions about gene therapy's potential to live up to the expectations of a cure. It also argued that the phrase "gene therapy" is in fact used to refer a range of different techniques, including approaches that are currently not beyond pre-clinical research stages, such as gene editing (9). Therefore, it is plausible that this discrepancy between wishes and perceived reality is a reflection of interview participants using the term gene therapy to refer to different things: either the overall program of gene therapy or specific AAV-mediated gene transfer methods that will shortly enter the clinic. This could explain how they simultaneously embrace the promises of gene therapy but would forego current products.

This may also explain why other studies found that most of their participants would be interested in having gene therapy for themselves or their child, while only roughly 30% of these participants considered themselves knowledgeable about gene therapy (19,20). It can be hypothesized that the participants in these studies reflected on a more general notion of gene therapy, whereas several participants in our study had knowledge of trial results.

Several authors have argued for the importance of educating people living with hemophilia about gene therapy, to allow them to make an informed decision (20,21). We would add that for such education to be most effective, it would have to differentiate clearly between different forms of gene therapy and their potential, rather than educating people about a general idea of gene therapy.

Increasing autonomy

This study identified freedom and independence as important outcomes for people living with hemophilia. Another interview study found that 'liberation' and 'control' were important outcomes of gene therapy for people living with hemophilia (22). All these concepts are related to the value of personal autonomy, which refers to a state of self-governance: having the possibility to act free from controlling influences and limitations (23). This suggests that finding ways to increase the autonomy of people living with hemophilia is beneficial to their quality of life. Similarly, others have suggested that the concept of a 'hemophilia-free mind' can be used to guide future hemophilia care (24).

Increasing autonomy does not solely have to be achieved through new treatments, and our results suggest that it also cannot be reached by adopting innovative therapies exclusively. This study shows that the extent to which gene therapy can achieve the desired goals partly depends on the social structures and policies in which the therapy is embedded, as well as the behaviors that the therapy elicits. Whether increased freedom is achieved depends on the rules that the treatment centers adopt and the frequency of follow-up visits required. Similarly, whether gene therapy effectively decreases the number of bleeds people suffer is dependent on the level of care and precaution they continue to take. Therefore, obtaining most value from gene therapy will require embedding the treatment in practices of care that foster autonomy through other means as well.

Hemophilia identity

In contrast to earlier findings of (academic and journalistic) research (25,26), our study did not identify fear of impacts on personal identity as an important topic for people living with hemophilia. Nevertheless, it was a topic that some respondents talked or joked about, indicating that it is a known phenomenon within the hemophilia community. Furthermore, many respondents told stories about how hemophilia

had shaped their lives. This suggests that at least for some of the people affected, hemophilia has had a role in shaping in their identity, a finding that is consistent with several other qualitative studies (27,28).

While conducting the interviews, it became clear that people use the term 'identity' to refer to different things; for instance to what they called 'identity politics', their experience of being themselves, or their character. Within philosophical literature, identity can be conceptualized in different ways as well (29). Previous research suggested that the fear of a change in identity experienced by some people living with hemophilia results from the 'burden of normality' (25). The burden of normality describes the experience of patients who have difficulty adjusting to a symptom-free life after a treatment, a phenomenon that has mainly been observed for patients with epilepsy or Parkinson's disease who have been treated with Deep Brain Stimulation (30,31). Alternatively, although our results do not provide clear evidence for this, it can be hypothesized that the fear of a change in identity results from the feeling of no longer being part of a hemophilia community, comparable to how being part of a community is an important aspect of d/Deaf identity (32). Several of our respondents indicated that after their liver transplantation, they became less active in the patient community, a community within which they had developed friendships, but none of them reported having experienced this as negative or impacting their identity.

Strengths, limitations, and recommendations for future research

Although our research design allowed for the inclusion of participants with a variety of backgrounds, there are some aspects for which there was homogeneity among the respondents. First, although we included several people living with hemophilia who would currently not consider gene therapy for themselves, there were no people who were generally opposed to gene therapy. Second, many respondents mentioned that they participated in this study because they considered it important to contribute to science or the further development of gene therapy. As a result, there might be a bias towards people with a relatively positive attitude toward genetic therapies and a high level of trust in science in our study. Third, although we included people living with hemophilia B who participated in a trial and a parent of a child with hemophilia B, our sample did not include people living with hemophilia B who did not receive gene therapy. It can be hypothesized that people living with hemophilia B have a more positive attitude towards gene therapy than people living with hemophilia A, as there is no subcutaneous treatment available for hemophilia B and recent research indicates that gene therapy expression is more stable and durable for hemophilia B than for hemophilia A (10). However, this is something that needs to be explored in further research.

Nevertheless, our research offers insight into a wide variety of stakeholders' opinions on hemophilia gene therapy and identified challenges that can occur when gene therapy becomes part of the standard treatment arsenal. The incorporation of a validation meeting allowed us to check our preliminary results for accuracy and adapt our topic list to incorporate more detailed questions on identity.

Our results provide several directions for future research. To begin, it would be valuable to find ways to foster autonomy in treatment to improve the quality of life for people living with hemophilia. Furthermore, it will need to be investigated whether people living with hemophilia experience identity issues when gene therapy enters the market, and if so, how they could be supported in the best way.

In addition, although we excluded the topic from the current study, the costs of gene therapy are an important topic for further research. As our results indicate, stakeholders have concerns about the fair distribution of gene therapy because of the expected high costs. Recent history indicates that such worries are not unreasonable. For instance, Bluebird Bio, which develops gene therapies for several disorders other than hemophilia, recently withdrew its licenses from the European market after not reaching an agreement over reimbursement with governments. Similarly, the gene therapy Libmeldy, for metachromatic leukodystrophy, will not be covered by Dutch health insurance because the costs are too high, making it inaccessible to patients (33). This indicates that the pricing and payment structures of gene therapies might also limit their accessibility in high income countries.

Conclusion

As gene therapy for hemophilia is developing rapidly and the first products are currently entering clinical care, it is important to explore the ethical issues that gene therapy raises. We have shown that freedom and independence, trust and altruism, and incremental benefits are important ethical considerations for stakeholders. Our study indicates that although people living with hemophilia embrace the general promises of gene therapy, the products that shortly enter the market are not necessarily considered to be superior to the current standard of care. People living with hemophilia wish to become more autonomous, which cannot solely be achieved through gene therapy. Furthermore, although becoming hemophilia-free has had an impact on the (social) lives of some people living with hemophilia, our study does not indicate that people living with hemophilia experience or fear a change in identity as a result of gene therapy. The insights obtained help to guide the further development of gene therapies and their introduction into society in a responsible manner.

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Supplementary file: Topic list

Introductie

- Kunt u wat vertellen over de invloed die hemofilie heeft op uw leven/op het leven van uw kind? / Kunt u wat vertellen over het werk dat u hier doet?

Voordelen & risico's

- Hoe ervaart u de huidige behandeling?
- Wat verwacht u van gentherapie?
- In hoeverre zijn die verwachtingen uitgekomen?
- Ziet u risico's aan gentherapie? Zo ja, welke?
- Zou u zelf willen overstappen? Waarom wel/niet?
- Bij wat voor resultaat en risico zou u het de moeite waard vinden?

Trials & follow-up

- Zou u aan een gentherapietrial meedoen? Waarom wel/niet?
- Zouden er ook trials met kinderen gedaan moeten worden?
- Er zijn mensen die pleiten voor lange-termijn follow-up van mensen die gentherapie hebben ontvangen. Hoe staat u daartegenover? Hoe zou dat eruit moeten zien?

Informed consent

- Denkt u dat mensen die meedoen aan een trial goed begrijpen waar ze zich voor hebben aangemeld?
- In hoeverre denkt u dat vertrouwen in de behandelaar een rol speelt bij de keuze om mee te doen aan een trial?
- Wat vindt u daarvan?
- Wat vindt u ervan als de eigen behandelaar het inclusiegesprek doet?

Impact identiteit

- Is iemand die gentherapie heeft gehad volgens u nog iemand met hemofilie?
- Stel dat u 80% factor 8/9 hebt, zou u dan lid blijven van de NVHP? Hoort zo iemand er dan nog bij?
- Hoe ervaart u het dat deze gentherapie er niet toe leidt dat hemofilie niet kan worden overgedragen aan uw kinderen? In hoeverre heeft dat een rol gespeeld in afweging wel/niet mee te doen aan onderzoek?

Gentherapie als behandeling

- Hoe zou de zorg voor iemand met hemofilie na gentherapie eruit moeten zien?
- Als gentherapie op de markt komt, aan wie zou het dan aangeboden moeten worden?
- Als gentherapie op de markt komt, verwacht u dan nieuwe risico's of problemen?

Overig

- Wilt u nog iets kwijt waar ik niet naar gevraagd heb?

CHAPTER 4

People with hemophilia as data coordinators: an analysis of the ethics and feasibility of self-management with personal health records

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Designed and drafted the chapter together with MB; revised based on comments from co-authors.

Abstract

Background: People living with hemophilia perform various self-management tasks, supported by multiple health apps. Upcoming personal health records enable individuals to access and add health information from different institutions in a single digital tool, providing an integrated overview of data. Later, individuals will also be able to share their data with health care providers and relatives. Yet, this creates a new role for users: coordinator of data exchange.

Objective: To analyze if and how personal health records contribute to self-management, with a particular emphasis on the role of coordinating data exchange.

Methods: We applied various interpretations of self-management to the promises of personal health records, to identify what goals it intends to achieve. We then assessed various skills and responsibilities that are required from users to work with personal health records. Last, we analyzed potential scenarios of the coordination of data exchange.

Results: Personal health records promise to support both compliant self-management (i.e. managing care conform medical regimens) and concordant self-management (i.e. managing care according to personal values and goals). Which of these forms is promoted depends on the goal of data coordinating tasks. Although the many (self-management) skills needed to work with personal health records may make them inaccessible to some, the chosen design for the data sharing feature may mitigate some.

Conclusion: It needs to be more explicitly defined what form of self-management is promoted by personal health records. A participatory design strategy can ensure that the design of coordinating data exchange matches individuals' and health care providers' needs.

Introduction

People with chronic and/or complex health conditions, such as hemophilia, often perform various self-management tasks. People who are severely affected by hemophilia are at risk of experiencing spontaneous joint or muscle bleedings that may result in joint damage, for which life-long monitoring and treatment is required. To prevent bleeds, regular self-administered prophylactic infusions are necessary. In case of a bleed, individuals administer treatment according to their individual treatment plan, with remote advice provided by healthcare providers. Other self-management tasks include: registering medication administrations in a digital journal (1), filling in questionnaires in an app, ordering medication, and checking laboratory results in a patient portal to monitor their condition.

To facilitate these self-management tasks, individuals can make use of several health apps as well as patient portals, offered by most health care institutions. As a result, individuals receiving care in multiple institutions must access different patient portals, with limited to no data exchange between them. The use of multiple apps and patient portals may result in an experienced lack of overview and control, which can be especially challenging for (older) people living with hemophilia with comorbidities, who may have up to fifteen different health care providers working in multiple care institutions (2). Since is often assumed that access to health information enables individuals to better monitor their condition(s) and treatment(s), an easy and comprehensive health overview is needed (3–5).

Personal health records combine information from multiple care providers in one website or app, thereby offering individuals a complete overview of their health information (6,7). Although still under development, it is expected that one personal health record can replace the numerous patient portals and health apps currently utilized by health care recipients. Consequently, people with a chronic and/or complex condition such as hemophilia are often considered the primary beneficiaries of the personal health record (8,9).

Personal health records are intended to offer three distinct features: viewing, adding, and sharing health information (10). First, personal health records promise individuals integrated access to all relevant health information from all health care institutions in one website or app, regardless of the care institution they are treated in, as illustrated in Figure 1 (6,7). Second, health care recipients can add information, including self-measurements, questionnaire responses, a treatment diary, or data from connected wearables. Individuals can either add data at their own initiative or on request of health care providers. Third, in the future, personal health records aim to enhance health care recipients' control over their data, by enabling them to share their digital data with family members, caretakers, and health care providers (9). The coordination of data exchange, which requires determining what health information may be viewed by whom, is a new role for care recipients (11–15). This new role aims

to increase health care recipients' level of self-management. This goal of personal health records is the most contested among stakeholders (16).

In this paper, we identify several ethical and practical questions that arise when care recipients use a personal health record. In doing so, we intend to add to the debate on the responsible development of personal health records, and more specifically, its data sharing feature. While personal health records are being developed in many countries (17,18), few countries have formalized the development and implementation of personal health records as extensively as the Netherlands (19). Therefore, we will focus on the situation in the Netherlands.

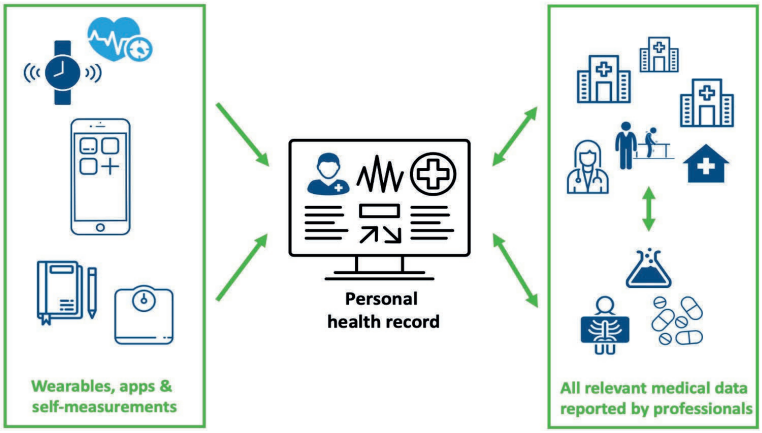

Figure 1: Schematic representation of the personal health record

Methods

We first provide an overview of the discussions surrounding self-management and apply these to the use of personal health records by people living with hemophilia. Based on this, we raise the question what goals self-management through personal health records aims to achieve, and how these goals may actually be supported by personal health records. We then discuss several skills that users of personal health records need to have, and evaluate its impact on the accessibility of these tools. Last, we critically assess the different options under consideration for the design of the data sharing feature and we end by suggesting an alternative variant.

Results & Discussion

Identifying the goals of self-management

Self-management in health care is defined as "an individual's ability to detect and manage symptoms, treatment, physical and psychosocial consequences, and lifestyle changes (such as exercise and diet) inherent in living with a chronic condition" (20, p.244). Increasing self-management in health care is considered to be desirable for

several reasons, such as: more efficient disease management, leading to a decrease in health care costs; the contribution of self-management to patient autonomy and independence; and health care recipients' unique first-person perspective to their body and life, which is essential to effective disease management (12,21).

Self-management can comprise many different activities, from administering prophylactic treatment, to checking test results and uploading self-measurements. Three forms of self-management are distinguished in the literature (14). In the first, individuals take over practical tasks and responsibilities from healthcare professionals (12). For people living with hemophilia, this includes tasks such as administering prophylactic medication as prescribed and recording treatment and bleeds in a digital treatment journal. In this form of self-management, individuals' own views are not involved, nor is any decision-making required from them (12).

In the second form, referred to as compliant self-management, individuals learn to manage the disease or condition on their own. This includes learning to interpret bleeding symptoms and health data, and knowing how to act in response. This form of self-management increases individuals' independence from their health care provider but does so in a way that mainly promotes compliance to medical regimes (12). Many of the telehealth interventions currently developed for the self-management of hemophilia aim to promote such adherence to treatment plans (22).

The third form of self-management, referred to as concordant self-management, describes a form of self-management in which individuals are enabled to find their way of living with the condition according to their personal views, values and goals (12). Importantly, these do not have to overlap with what is optimal from a medical perspective (12).

It has been argued that successful self-management can be achieved through empowerment (20). There is no consensus, however, on how empowerment should be conceptualized and what it entails in relation to digital health tools (23–27). Although there are ambiguities, patient empowerment is generally considered to be desirable and understood to be a process or a state wherein health recipients have or obtain the ability to take control over their health and well-being, rather than ceding such control to a healthcare provider (25,27,28).

It is left unspecified exactly how this control is gained (24). In the literature on digital health tools, it is often presumed that obtaining more information will lead to more control (15,24). Different authors describe various attributes that are required to obtain this control, such as having sufficient knowledge, skills and self-determination (25,26,28). Many digital health tools, including personal health records, have as one of their most important aims to provide health care recipients with information. However, increasing the amount of information is not sufficient for increasing care recipients' knowledge or their ability to make and execute choices regarding their health (15,24). Furthermore, it is generally argued that obtaining control over health

requires more than control over circumstances and the ability to make choices (24,26). Therefore, some authors argue that digital health tools may primarily give users the feeling of being empowered, while empowering effects are often disproportionate to the burden of additional responsibilities assigned to users (15).

It is generally assumed that personal health records will increase health recipients' self-management and support them to become empowered. It is said that through easier, integrated access to health information, personal health records may increase health knowledge and disease insight (8,9,16,29,30), help people to better consider their own preferences, wishes and values (9), facilitate disease management (8,9,16,29), and enable individuals to take on a more pro-active role in and increased control over their health care (29).

Based on the literature on personal health records, it appears personal health records aim to support both compliant and concordant forms of self-management, by assuming individuals will adopt a healthier lifestyle and simultaneously supporting them to live a life according to their own values and goals. However, these aims can easily compete with each other, since pursuing one's own goals does not necessarily imply pursuing goals that align with medical advice. For instance, people living with hemophilia might aspire a career as a police officer, or desire to play a game of rugby. Making other decisions than prescribed by health care providers or an individual's refusal to take on certain tasks or responsibilities can also be an expression of their autonomy and a sign of empowerment (14,20).

Furthermore, it is questionable if control over data sharing aims to support the same goals and values as control over health does. Control over data sharing is not as directly related to health outcomes or the ability to live a life according to one's views, which are some goals of increasing self-management in health care. Instead, control over data coordination aims to increase privacy and insight in the availability of data (31).

There should thus be a more explicit recognition of the exact goals of self-management, and how the personal health record aims to support these. Crucially, supporting concordant self-management also means that people living with hemophilia should have the opportunity to refrain from using a personal health record if they want to.

Skills required for becoming a "data coordinator"

Data coordination requires several skills and knowledge to successfully lead to empowerment. In particular, four forms of literacy can be distinguished that are relevant to the use of personal health records (32,33). First, general literacy refers to the ability to read written text and to understand the language it is written in, as well as numeracy skills (32,34,35).

Second, computer and mobile device literacy refers to skills needed to access the internet, use a computer or mobile device, or perform online authorization for government and health services (36). To exercise computer skills, people need to have sufficient fine motor skills (needed to use a mouse, keyboard or phone) and have no clinically relevant visual impairments (34).

Third, health literacy is defined as "people's knowledge, motivation and competences to access, understand, appraise and apply health information in order to make judgments and take decisions in everyday life concerning healthcare, disease prevention and health promotion" (37). In the coordination of data exchange, this also requires an understanding of the demarcation of medical specialties (i.e. what parts of the human body does a urologist treat) and which professionals collaborate in shared care, and what information is relevant for health care providers' medical reasoning process. Fourth, information literacy refers to people knowing how information is organized and how to find information (32).

Due to these essential skills, as well as the required effort, responsibilities and understanding, the use of a personal health record may be less accessible to some people than to others (13,14). This may exclude certain groups. This is a risk that arises with many digital health tools (11).

Two scenarios for data exchange coordination through the personal health record

In addition to integrating digital self-managing tasks, personal health records also aim to increase self-management in a new way, by enabling coordination of data exchange. As a result, individuals will then become "data coordinators" of their health care data (9,29). No personal health records currently enable this.

Currently, health care recipients can view their medical record digitally and have the right to request removal or correction of health information in medical records, which health care providers approve on a case-by-case basis (38). However, care recipients are not able to electronically share their data with health care providers pro-actively. Consequently, health care providers can only directly access health information reported by their colleagues in three situations. First, if colleagues work in the same care institution and therefore use the same electronic health record. Second, if there is presumed consent of individuals (e.g. an individual agrees to be referred to another health care provider). Third, if two health care providers work together in treating the same condition (e.g. shared care) (39–41). In all other cases, care recipients must first approve data exchange. As a result, the required information can often only be accessed after a first consultation, although access to health information is essential for health care providers' medical reasoning and (shared) decision making.

For the design of data sharing in the personal health record, two potential scenarios are considered by legislative parties, each with its advantages and

limitations (42). In the "active" design scenario, individuals are given the option to proactively share health data with health care providers. Individuals may determine the recipient of health information (e.g. general practitioners, hospitals, mental health facilities), what information is shared (e.g. medication, treatment plans), or both (43). In this "active" scenario, prior to a consultation with a health care provider, health care recipients need to independently determine which information to share and not to share, by assessing what information would be of interest to a particular health care provider.

In contrast to the "active" design scenario, in the "passive" scenario, a health care provider asks individuals to share (part of) their health data prior to a consultation (42). Instead of leaving it to care recipients to assume what information is important to a certain health care provider, it would be the health care provider's responsibility to determine and communicate which information is relevant for them. Individuals would then only decide to share or not share the requested information. Yet, this would require health care providers to determine, well in advance of a consultation, what information might be relevant to them, and would require individuals to respond to these requests. It is uncertain if this is feasible for health care providers.

Instead of each of these designs, a hybrid scenario, combining the two designs, might work best. In a hybrid design, an active scenario for general health information may be combined with a passive scenario for disease-specific information. For general health information, such as medical history, medication prescriptions and medication administrations, health care users would be asked to pro-actively determine the recipient (e.g. general practitioner, hospitals). Consequently, individuals would only receive passive requests from health care providers to share disease-specific information (e.g. a hematologist has asked a person with hemophilia to record bleeds in a digital treatment diary). Individuals would still be able to refrain from sharing health information after discussing this with health care providers on a case-by-case basis.

Nonetheless, several challenges associated with the role of data coordinator will remain in a hybrid design, such as those related to health recipients' skills, literacy and the transfer of responsibilities (44). Counselling individuals on data sharing decisions may help to strengthen their self-efficacy (i.e. the belief to be able to successfully execute self-management tasks) (45,46), resulting in less hesitancy over data sharing choices and reduced stress (47,48).

Conclusion

By offering individuals easier, integrated access to health information and more control over the exchange of these data, personal health records aim to increase individuals' self-management. This may especially benefit individuals with chronic and/or complex health conditions, such as hemophilia. We evaluated if and how

personal health records can achieve this goal, by distinguishing between compliant and concordant self-management. Which of the two forms is primarily supported partly depends on the goals of increasing self-management. These may include, but are not limited to, increasing efficiency in health care, supporting patient autonomy, and increasing privacy. The goals need to be better defined before data sharing through the personal health record can truly aid empowerment. Furthermore, there may be differences between skills and wishes of various health care recipients, which need to be accommodated. Therefore, we recommend a participatory design strategy, to determine the best design scenario for data sharing in the personal health record, and to ensure individuals receive sufficient support to make decisions on data sharing.

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CHAPTER 5

What is a cure through gene therapy? An analysis and evaluation of the use of "cure"

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Abstract

The development of gene therapy has always come with the expectation that it will offer a cure for various disorders, of which hemophilia is a paradigm example. However, although the term is used regularly, it is unclear what exactly is meant with "cure". Therefore, the aim of this paper is to analyze how the concept of cure is used in practice and evaluate which of the interpretations is most suitable in discussions surrounding gene therapy. We analyzed how cure is used in four different medical fields where the concept raises discussion. We show that cure can be used in three different ways: cure as normalization of the body, cure as obtaining a normal life, or cure as a change in identity. We argue that since cure is a practical term, its interpretation should be context-specific and the various uses can exist simultaneously, as long as their use is suitable to the function the notion of cure plays in each of the settings. We end by highlighting three different settings in the domain of hemophilia gene therapy in which the term cure is used and explore the function(s) it serves in each setting. We conclude that in the clinical application of gene therapy, it could be better to abandon the term cure, whereas more modest and specified definitions of cure are required in the context of health resource allocation decisions and decisions on research funding.

Introduction

The development of gene therapy has always come with great expectation of being able to offer a cure for various disorders (1). One of the paradigm examples of this promise stems from the field of hemophilia care. Hemophilia is a congenital bleeding disorder that leads to spontaneous bleeding into muscles and joints if left untreated. Because hemophilia is a single-gene disorder with a wide therapeutic window, it has traditionally been perceived as the ideal model for validating general gene therapy principles (2,3). After several decades of research, the first gene therapies for hemophilia A and B have received market authorization by the EMA and FDA. Simultaneously, further research and development of gene therapies for hemophilia is ongoing.

In contrast to many other disorders for which gene therapies are being developed, several treatment options are already available for hemophilia (4,5). As a result, the life expectancy of people living with hemophilia in resource-rich settings is approaching that of the general population (6,7). Therefore, for people living with hemophilia living in resource-rich settings, gene therapy is likely to become a personal choice in the palette of treatment options.

In the literature, several arguments in favor of the further development of gene therapies for hemophilia can be recognized. Most regularly mentioned are the expectations that it will circumvent many of the burdens of current treatment, lead to cost savings and will provide cure (8–11). Particularly the latter promise, the ability to provide cure, is embraced and used in headlines in both academic literature and news media discussing trial results (12,13).

However, it remains unclear what is meant when cure through gene therapy is promised. Several authors mention the potential of gene therapy to cure, but do not offer any definition or explanation of the concept (e.g. 14,15). Further, empirical research indicates that people living with hemophilia and their health care providers differ in their opinion whether a cure has been achieved after receiving gene therapy in a trial (16). Therefore, the aim of this paper is to analyze how the concept of cure is currently used in practice and evaluate which of these uses is most suitable in discussions surrounding gene therapy for hemophilia.

Method

The concept of cure is elaborated on rarely in the philosophical literature. However, according to its definition in the Oxford dictionary, cure is concerned with restoring health. It is therefore helpful to look at the debate on the concepts of health and disease. There is a longstanding theoretical debate on health and disease, and several competing theories have been formulated to explain their meaning and function (17–19). In more recent contributions to this debate, health and disease are no longer considered to be theoretical concepts, but practical terms, that fulfill a certain

function in a given context, for instance in different academic disciplines, in different institutional settings in society or in different health practices (20–23). Because they are practical concepts, it has been argued that standard conceptual analysis is ill-suited to understand their meaning (20,22,24). It is therefore argued that instead of searching for final definitions with necessary and sufficient conditions, the debate should focus on developing multiple context-dependent definitions, that each have their own merit in a certain context or institution (20–22).

Based on these insights, we will treat the notion of cure as a practical concept as well. We proceed in two steps. First, we aim to obtain insight into the differing ways in which the concept of cure is currently used in practice. We do so by examining how the concept of cure is used in various medical fields in which the concept of cure is contested and therefore regularly discussed: oncology, psychiatry, care for people with a hepatitis C virus (HCV) infection and care for d/Deaf people. These fields were chosen because of the diversity in the type of pathology they are concerned with and the variety of patient groups involved in each of the fields. We have included a variety of literature discussing cure in each of the fields, including reviews, qualitative studies, and argumentative papers.

Second, we turn to the debate on gene therapy for hemophilia. In section 4, we apply the identified uses of cure to the debate on gene therapy for hemophilia. In section 5, we distinguish three different settings in which the notion of cure is used in relation to gene therapy and discuss factors that are important to take into consideration when using the concept of cure in a certain setting. Accordingly, we evaluate which of the interpretations of cure is most suitable.

Use of the concept cure

The term "cure" is used regularly, although it is often left undefined. However, based on a review of uses of cure in the literature on the abovementioned fields and discussion within the research team, we identified three different interpretations of cure: cure as normalization of the body, cure as obtaining a normal life, and cure as a change in identity. We also discuss situations in which the use of cure is deliberately avoided.

Cure as normalization of the body

When an explicit definition of cure is provided in the medical literature, it often refers to cure as some way of normalization of the body (e.g. 25–27). An example of this is the promise of cure through regenerative medicine, as regenerative medicine promises to "replac[e] or regenerat[e] human cells, tissues or organs, to restore or establish normal function" (25). Many of these definitions have an instrumental purpose, as they are developed to be able to compare the outcomes of different treatments options. Therefore, they incorporate an element of temporality, whereby

cure is defined and assessed over a period of time after treatment. For instance, in oncology, cure can be defined as no return of cancer for at least five years after treatment (26). Similarly, in the treatment of HCV infection, cure is often defined as sustained virological response (SVR) at 24 weeks after treatment (27,28).

The definitions of cure mentioned above are applicable to the level of the individual patient. In contrast, cure can also be defined on a population level. This use is also common in oncology, where a "statistical cure" for cancer "implies that the mortality rate of people diagnosed with a certain neoplasm returns to the level expected in the general population of the same sex and age, or, equivalently, when the excess mortality rate approaches zero" (26).

The idea of normalization of the body has received criticism from the field of disability studies, where it is argued that the focus on normalizing bodies does not value the lives and bodies of disabled people (29).

Cure as obtaining a normal life

Cure is also used to describe a normalization of various aspects of daily life. This idea recurs often in literature on patient experiences and wishes of treatment for HCV infection, in particular HCV obtained through injective drug use (30–32). It is argued that in general, cure is understood to mean an end to illness and its effects, as well as restoration of a prior state of health and well-being, as a result of which cure is seen as an endpoint (31). Many people with HCV express the hope that a cure will allow for a return to normality (30,32). Because globally, people who inject drugs and people in prison are the two main groups affected by HCV, overcoming social stigma is an important part of cure for these patients (30,33). However, this understanding of cure is criticized, because the focus of cure as end-point overlooks the ongoing experiences, needs and suffering of people after the completion of treatment (31).

In oncology literature there is also reference to "our shared belief about what a cure really is", namely "the idea that at some point after treatment, one's life is no different than someone who had not experienced that disease" (34). Further, in the fields of both oncology and HCV treatment, it is also recognized that the ability to obtain a normal life also relates to laws, policies and social structures, such as access to insurance or governmental benefits, and cannot be solely achieved by biomedical cure (31,35–37).

Cure as a change in identity

Finally, cure is conceived as a change in identity focusing on how both the illness experience and the transition to a state of health can become integrated into a person's narrative identity. This interpretation can be recognized in qualitative research on experiences of people with an HCV infection. This research indicates that many people, especially people who contracted the infection through injecting

drugs, value a cure for several outcomes other than "sustained virological response", such as its impacts on identity and social connections (32). As the authors define cure as sustained virological response, they describe the other outcomes as "beyond cure" (32). This group in particular hopes that clearing the HCV infection would lead to a positive change in identity, which would also help them to leave the label and stigma of "drug user" behind. Therefore, for several people living with HCV infection a cure would not mean a "return to normality", but a "reawakening" or "rebirth" (30). As a result of these high expectations, some people were disappointed by the effects of a cure for HCV infection, as they thought it did not live up to the promises and hype (32).

Similarly, it has been argued that the distinction between technology that is assistive and curative does not arise from the form or function of the technology, but from the role the technology plays in establishing the user's relational narrative identity as either belonging to the social group of people with a disability or disease or the social group of people without a disability or disease (38).

The discussion surrounding a change in identity also recurs among people with various disabilities. For instance, for some d/Deaf people, deafness is seen as part of who they are and the social group to which they belong (39). Therefore, some consider the idea of cure for deafness undesirable (38).

Alternatives to cure

In both the fields of psychiatry and oncology, some authors argue that the notion of cure should be abandoned, as it is thought a cure is unreachable and the focus on cure is not beneficial for the quality of care. For instance, in psychiatry, there is a growing movement arguing that mental illnesses are seldomly cured, and should be considered "vulnerabilities" rather than "diseases" (40). Instead of focusing on cure, it is argued that psychiatric care should focus on "recovery" or "healing" (40–43). These concepts are not focused on "getting better" or "becoming normal", but mainly focus on well-being, resilience, and the ability to adjust to and manage challenges, which can be achieved by having attention for the relational, narrative, ritual and metaphorical aspects of care (40,42–46).

Similarly, in oncology, although the term cure is used abundantly in the literature (34), in practice, many oncologists are hesitant to tell a patient they are cured, because of a lack of confidence about the risk of relapse (37,47,48). Instead, terms like "in remission" or "no evidence of disease" are used in cancer care (37). Furthermore, without the possibility of being able to speak of "cure", people living with a history of cancer often choose to speak of "cancer survivorship", as they prefer not to be called patients (49). The term cancer survivorship is used from the time of diagnosis throughout the rest of life. The concept draws attention to the phases of care required after active cancer treatment and also includes the health effects and emotional toll of a cancer diagnosis on family members, friends and caregivers (50).

Cure for hemophilia

Although the concept of cure is often used without being defined in care for hemophilia, each of the abovementioned uses of cure can be recognized in the field. To start with the most stringent definition of cure: "complete correction of previous bleeding tendency with normalized clotting factor levels 5 years after curative treatment, requiring no further treatment (with coagulation factor or other treatments), not even for surgery or bleeding. Cure is phenotypically intended and does not include: eliminating transmission of hemophilia to children or fully reverting established damage" (51). This definition is focused on normalization of the body, and, as the definition was developed to be able to compare outcomes of different treatment options, also incorporates an element of time (51). Similar definitions of normalization of the body through the criteria of elimination of bleeding and not requiring prophylactic treatment can also be recognized in other uses of the term cure (12).

Simultaneously, cure is also used to refer to obtaining a normal life. For instance, Skinner et al. argue that there are several "interrelated cure issues", that also entail lost education and career opportunities and financial consequences (2004, p.115). Similarly, the concept of a "hemophilia-free mind", defined as the absence of psychological burden and of permanent thoughts about hemophilia and its complications, has been suggested as a goal for further development of hemophilia treatment (53,54). It has been argued that the concept of a hemophilia-free mind should also be applied to family members taking care of or living with people living with hemophilia (55). Although the authors do not relate a "hemophilia-free mind" to the concept of cure, the idea of not having to think about a disorder is part of having a life unaffected by the disorder, comparable to how a cure as obtaining a normal life is understood.

Finally, the idea of cure as establishing a change in identity can also be recognized. In the literature on hemophilia gene therapy, cure as establishing a change in identity is discussed in accounts of people living with hemophilia who do not desire to receive gene therapy because they do not want to lose the identity of being a person with hemophilia (56,57). For these individuals, the notion of cure as corresponding to a change in identity is undesirable.

In the discussion surrounding gene therapy for hemophilia, we did not encounter any arguments in favor of abandoning the term cure or proposing alternatives to use in its place.

Gene therapy and the role of cure

In this section we highlight three different settings in which the term cure is used in relation to gene therapies, particularly gene therapy for hemophilia, and look at the role the concept can play in each of these settings. We do not claim to provide

an exhaustive overview of the different settings and practices in which the concept is used, but provide a starting point for thinking about the role and function of the concept of cure in relation to gene therapies.

Cure in the clinical application of gene therapy

One evident context in which the term cure is used is in a clinical setting, where patients may receive gene therapy as part of research or care. "Cure" can here be used as a goal for or outcome of treatment. In a setting in which people decide whether to opt for gene therapy, it is important that they have the right information to make an informed choice. Therefore, use of the word cure, or potential cure, as gene therapy is often described, may create wrong expectations if it is not clear what is meant with the term, or if patients attach a different meaning to the word than their physicians do.

In both clinical care and research, specific endpoints are defined in order to be able to measure effectiveness. Often, such endpoints do not include a more abstract notion such as "cure". Nonetheless, the definition of cure by Van Balen and colleagues, mentioned in section 4, is aimed to be used as a standard in outcome. However, as the definition explicitly excludes eliminating transmission to offspring or reverting established damage, it might not live up to the expectations of people living with hemophilia who understand cure to mean a normalization of their life or a change in identity.

This indicates that cure may have a different meaning for various people living with hemophilia. This is also supported by qualitative research we have conducted. Our interview study found that clinicians and people living with hemophilia sometimes differ in their opinion on whether people are cured after gene therapy, and that some people living with hemophilia have expectations that are unrealistically high according to their physician (16). The term is thus used ambiguously in the field, which could lead to unclarity between stakeholders or in conversations between people living with hemophilia and their health care providers.

Furthermore, after having received gene therapy and potentially having obtained normalized coagulation levels and bleeding symptoms, which could be considered a form of cure as "normalization of the body", many people living with hemophilia will still experience complications from the disorder. People living with hemophilia often have joint damage resulting from earlier bleeding, which will progress and continue to impact quality of life (58). Similarly, because hemophilia is a congenital disorder, it can still be passed on to future generations, people living with hemophilia have only ever known life with hemophilia, and usually they have several stories of living with hemophilia among their relatives. Therefore, no longer having hemophilia will never be a "restoration" of a previous state of health, but will likely resemble a state of being in which people do not have to worry about bleeding, but still live with the consequences and previous experiences of living with hemophilia will remain.

Therefore, in interactions between people living with hemophilia and health care providers, it might be desirable to refrain from using the term cure, and instead opt for merely using specific endpoints and effects on quality of life when discussing potential benefits of a treatment or trial. Furthermore, because people may still need some form of medical care after gene therapy and it is uncertain whether gene therapy has a long-lasting effect, a term that describes life after treatment for disease, similar to the role the term "cancer survivorship" plays, could be most suitable to describe the period after having received gene therapy. This could prevent confusion and thereby improve informed decision making, and could also be a more accurate description of the life and care required after gene therapy. Therefore, in the patient-physician relationship, the physician should become aware of the patient's expectations of what a cure entails and what gene therapy can achieve, and critically assess to what extent this is a realistic expectation.

Cure in resource allocation decisions on gene therapy

The concept of cure also plays a role in decisions on resource allocation with regard to gene therapy. It has been argued that having a specified concept of disease is particularly important regarding questions when medical intervention is required and justified, including to be able to distinguish between treatment and enhancement, to prevent medicalization and in questions regarding distributive justice in health care (20,22,59).

Currently, the notion of cure is used in questions regarding distributive justice. For instance, in the Netherlands, there is a policy-instrument, the Coverage Lock (CL), that is used to evaluate new, expensive medicines before they are included in basic health insurance. The EMA-approved gene therapies for hemophilia A and B are currently undergoing the CL procedure. In the CL process for another gene therapy, Libmeldy to treat metachromatic leukodystrophy, the potential to cure was considered one of several arguments that together could make a higher price acceptable (60). Similarly, in the literature it is argued that therapies with a potential to cure may have a special value that justifies a high price (61,62). It has been suggested that such distinctive elements of value include liberation from disease identity, liberation from stigma, and liberation from the burden of ongoing treatment (61). In our analysis, these elements are not just part of the value of a cure, but also part of the conceptualization of a cure.

In decisions on reimbursements, it is important to be explicit about what is meant with a cure and in what ways a product with a potential to cure differs from other treatment options, to assess what added value a cure may bring. If cure is defined as a change in identity, it is questionable to what extent this is valuable for people living with hemophilia, as currently, it has mainly been described as an undesirable outcome. Cure understood as normalization of the body raises several

questions: should normalization also include restoring residual damage to joints? Should it include potential side effects of gene therapy? Furthermore, cure as obtaining a normal life is dependent on more factors than a treatment or medical intervention, such as persons' opportunities in life and their mental state. This means that before any of the uses of cure is valuable in decisions on reimbursement, several questions need to be answered.

Cure in the context of research funding decisions on gene therapy

The notion of cure is also used in trial protocols and research proposals for new gene therapies and other innovative treatments. For instance, a trial protocol mentions that gene therapy, in contrast to existing treatment options, offers the potential to cure hemophilia A (63). Other registered hemophilia gene therapy trial protocols do not explicitly mention the promise of a cure through gene therapy, but do mention that one of the downsides of current standard treatment is lack of a cure (64). This suggests that, although cure is not included as a study outcome of current gene therapy trials, it appears to be a goal of the program of gene therapy. As trials employ specific endpoints in order to measure effectiveness, if cure would be included as an outcome measure for a trial, it would have to be defined specifically and with a component of time (e.g. five years) in order to be able to serve as an endpoint to evaluate the effectiveness of an intervention. This suggests that cure as form of normalization of the body might be most suitable. Further, cure as obtaining a normal life or a change in identity relates more to quality of life, which is often used as a secondary endpoint in trials. If cure is considered to be one of the primary goals of gene therapy, it raises the question whether quality of life should also become a primary endpoint of trials rather than a secondary endpoint.

In contrast, in the development of research proposals, the notion of cure is often used as a more abstract promise of what the study will achieve. While working on research proposals, researchers regularly have to boost expectations in order to attract funding (65). As a result, the term cure can contribute to hype and high expectations surrounding gene therapy, which may increase further when cure is ill-defined or interpreted differently by various stakeholders. Therefore, although use of the term can be valuable in this setting, it is important to be hesitant when translating these promises to other settings.

Conclusion and future directions

The promise of cure appears to be closely tied to expectations of gene therapy. Simultaneously, the term often remains undefined or is used to refer to varying outcomes. Therefore, we analyzed how the term is used in several medical fields. We have shown that cure can be used to refer to at least three different outcomes of treatment: normalization of the body, obtaining a normal life, and a change in

identity. We have argued that since cure is a practical term, its interpretation should be context-specific and the various uses can exist simultaneously, as long as their use is suitable to the function the notion of cure plays in each of the settings. Without aiming to be exhaustive, we then highlighted three contexts in which the term cure is used. We argue that in the clinical application of gene therapy, it could be better to abandon the term cure, whereas a more modest and specified definition of cure is required in the context of health resource allocation decisions and decisions on research funding.

These considerations on the use of cure can provide more clarity and stimulate reflection in discussions surrounding gene therapies or other innovative treatments. Moreover, awareness of the various potential interpretations of cure should urge for carefulness when speaking of "cure", especially when the contexts in which the term is used meet or when stakeholders transcend the context in which they usually operate, as incongruent use of cure may cause misunderstanding and potentially unrealistic expectations.

This paper has provided insight into various ways in which the term cure can be understood and has argued that depending on the context, different interpretations might be more or less valuable. Thereby, the paper invites further deliberation on the contexts in which the term cure is used and provides input for the discussion surrounding the benefits of gene therapy.

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CHAPTER 6

Can hemophilia be cured? It depends on the definition

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Abstract

Over the years, the palette of treatment options for hemophilia has grown extensively, leading to an increased life expectancy and quality of life for people living with hemophilia. Nonetheless, it is frequently emphasized that none of the current treatment modalities provides a "cure". It is therefore hoped that innovative treatments such as gene therapy may bridge this void. However, the precise definition of a "cure" for hemophilia remains unclear. In this review, we show how the concept of cure is currently used in hemophilia. We then relate the discussion on cure to debates surrounding the classification of hemophilia and philosophical debates on the concepts of health and disease.

Introduction

Hemophilia is a rare, congenital bleeding disorder characterized by a lack of clotting factor FVIII (hemophilia A) or FIX (hemophilia B). If left untreated, the disorder leads to spontaneous or trauma-induced bleeding into muscles and joints (1). Hemophilia can also lead to unstoppable bleeding in essential organs after trauma or surgery, which means that without treatment many people living with hemophilia are likely to die during childhood or early adulthood (2). Over the past six decades, hemophilia has transitioned from a fatal disease whereby patients were not expected to live longer than 20-30 years to a manageable disorder with a life expectancy close to that of the general male population (3).

Nowadays, people living with hemophilia in resource-rich settings have access to a variety of treatment options. Standard of care consists of prophylaxis with clotting factor replacement products, requiring intravenous injections several times a week (4). From the 2010s, clotting factor products with an extended half-life have reached the market, thereby decreasing the number of injections required, and thus decreasing the burden of treatment (3). More recently, the non-replacement product emicizumab has become available for people living with hemophilia A, which can be injected subcutaneously and requires less frequent injections, once every one to four weeks. Other non-replacement, or rebalancing, products for hemophilia A and B are currently in development (5).

Although this array of treatment options has increased the quality of life for people living with hemophilia, it is often stated that none of these options provides a definitive cure. Therefore, many hope that innovative treatments such as gene therapy will fill this gap (3). At the same time, a consensus definition of cure for hemophilia is lacking (6).

In this paper, we show how the concept of cure is currently used in the field of hemophilia and relate it to the debate surrounding the classification of hemophilia that has recently unfolded. The paper consists of three parts. In section 2, we review the current use of the concept "cure" for hemophilia. In section 3, we discuss the current debate surrounding the classification of hemophilia and its relevance for discussions on cure. In section 4, we relate both debates to philosophical notions of health and disease. We end by highlighting some points that require consideration in the further debate on these concepts.

A "cure" for hemophilia

Numerous scholars highlight that gene therapy holds the potential to cure hemophilia. At the same time, they oftentimes do not explain or clarify what they mean by "cure" (e.g. 7–10). Some argue that "the possibility of curing, rather than simply controlling, the disease has been the holy grail of hemophilia treatment and is finally becoming a reality with gene therapy" (11). Others mention that "a gigantic unmet need was

the lack of a cure" (3). The promise of cure appears to arise mainly in relation to gene therapy, although some authors also mention how cell therapy (12,13) or liver transplantation (14,15) may provide a cure.

The use of cure in the context of outcome sets

The most concrete and elaborated definitions of "cure" for hemophilia are provided as part of sets of core outcome measures for the treatment of hemophilia. Several core outcome sets for hemophilia have been developed, each with a slightly different focus (16–20). Three of these sets incorporate cure as an outcome; these sets will be discussed below.

The coreHEM outcome set aims to determine a core set of outcomes to evaluate efficacy, safety, comparative effectiveness and value of gene therapy trials (19). CoreHEM has identified six core outcomes: frequency of bleeds; factor activity level; duration of expression; chronic pain; utilization of healthcare system; and mental health (19). Integration of all these elements collectively constitutes a cure for hemophilia. According to the authors, this interpretation of cure encompasses the entire spectrum of the functional and social impact of living with hemophilia (19).

Another core outcome set was developed by Van Balen and colleagues, focusing on health outcomes relevant to people living with hemophilia (18). This project has identified a list of ten health outcomes. Cure is one of these outcomes, next to: impact of the disease on life expectancy; ability to engage in normal daily activities; severe bleeding episodes; number of days lost (work or school); chronic pain; complications; sustainability of physical function; social functioning; and mental health (18). The authors provide a specific definition of cure as follows: "complete correction of previous bleeding tendency with normalized clotting factor levels 5 years after curative treatment, requiring no further treatment (with coagulation factor or other treatments), not even for surgery or bleeding. Cure is phenotypically intended and does not include: eliminating transmission of hemophilia to children or fully reverting established damage" (18).

A third outcome set, developed by Skinner and colleagues, defines a functional cure based on seven levels, with the goal of ultimately achieving health equity for all people living with hemophilia worldwide (20). The seven levels are considered milestones that people living with hemophilia can achieve successively, thereby describing a progressive definition of cure. The levels are: survival; minimal joint impairment; freedom from spontaneous bleeds; attain "normal" mobility; able to sustain minor trauma; undergo surgery or major trauma without additional intervention; and normal hemostasis (20). In parallel to the set of outcomes defining cure, a set of patient-reported outcomes to achieve health equity was defined, matching the clinical outcomes. These patient-reported outcomes are: prevent premature death; improved quality of life/participation in activities of daily living;

ability to engage in low-risk activities; participation in work, career and family without restriction; more unrestricted lifestyle; not dependent on specialized health care; optimized health and well-being (20).

Thus, based on these outcome sets, cure can be regarded in several ways, whereby some interpretations are broader than others. Cure may be seen as a correction of the bleeding tendency (18,20), or in addition to this also incorporating prevention of joint damage (20). The concept is also used in a more comprehensive way, whereby it includes the absence of chronic pain and the impact of hemophilia on a person's psychological state (19).

Characteristics of cure

In addition to the specific definitions developed as part of core outcome sets, several authors mention characteristics of a cure. Based on these descriptions, several aspects of a cure for hemophilia can be identified.

A first characteristic is its durability. Several authors mention that a cure is "permanent" (21,22), "definitive" (23), "lasting" (24), "lifelong" (25–27) or "durable" (28), or leads to "stable" (29,30) or "continuous" (31,32) expression of endogenous clotting factor. Several authors state that a cure is a single, or "once and done", treatment (15,28,33,34).

Based on the argument on 'durability', there is disagreement whether gene therapy has ever resulted in a cure. Some argue that it has, based on trial follow-up data of several months up to a few years (23,27,35–37). Others argue that the current lack of knowledge about the durability of gene therapy precludes a definitive conclusion on cure (38). Still others argue that the declining clotting factor levels seen in a number of gene therapy trials may be considered a "near-cure" (39).

Further, several authors mention that a cure leads to endogenous factor expression (29–32,40,41). For some, a cure entails factor expression in the normal range (50-150%) (12,42,43). Others state that curative levels do not have to equal normal levels or speak of cure when clotting factor levels have been raised to the mild or moderate range or when factor levels exceed 10% (27,44,45). It is also said that a cure leads to "symptom-relief" (46) or that cure entails being free of spontaneous bleeding (34,45,47) without requiring prophylaxis (45,47).

Finally, some authors emphasize quality-of-life related aspects of a cure. For instance, they argue that because the standard of care already leads to long-term survival, cure for hemophilia revolves around enhancing the quality of life throughout an individual's lifespan (6). Further, it is stated that cure goes beyond stopping and preventing bleeding, and is more concerned with normalizing the life of people living with hemophilia (48).

Cure and the classification of hemophilia

Over the last few years, a debate has developed regarding the classification of hemophilia (49–51). Given that the concept of cure refers in some way to a transition from having hemophilia to a state of health, the debate surrounding classification of hemophilia might be informative to better understanding the concept of cure. In this section, we will summarize this debate on classification and draw lessons from it.

According to the official guidelines of the International Society on Thrombosis and Haemostasis (ISTH), "plasma procoagulation levels, rather than clinical bleeding symptoms, should be used preferentially for the classification of hemophilia" (52). According to this classification, plasma factor levels of <1% of normal classify as severe, 1-5% as moderately severe, and >5%-40% as mild (52).

However, recently, Thachil and colleagues have argued that this does not do justice to clinical reality, given that coagulation factor activity levels do not always correlate with bleeding phenotype (49). In addition, they mention that different clotting factor assays differ in accuracy, thereby risking misdiagnosis when used as the sole source for classifying hemophilia into the categories severe, moderate and mild (49). Therefore, they argue for a shift in treatment target, away from a clinicians' perspective on the disorder to a focus on quality of life. Therefore, they propose that "those with significant symptoms are those with bleeding that negatively impacts HRQoL [health-related quality of life] issues and require an intensification of treatment to maintain hemostasis and keep secondary morbidities at bay" (49). In a second piece defending their original argument, the authors state that care for people living with hemophilia should be directed towards the WHO's definition of health as a state of complete physical, mental and social well-being (53).

This proposal has received both critique and support, which mainly seems to focus on the question of what the goal of disease classification is (50,51,53). Critics of revising the definitions of hemophilia severity argue that the goal of disease classification is correct prognostication and to allow patients to find and be treated by the correct physician, and therefore argue for the importance of distinguishing between prognostication and adopting an outcome-based treatment approach (50). Supporters of a revised definition emphasize the importance of the lived experience of people living with hemophilia and the sociopolitical effects of labels, e.g. regarding social policies developed based on such classifications and access to and reimbursement for treatment (49,51). These authors do not deny the importance of classification for selecting appropriate treatment and prognostication, but argue that a reclassification allows for a shift from provider-centered care to care centered on people living with hemophilia (51,53)

A similar discussion has unfolded surrounding the labeling of women and girls with a gene variant for hemophilia. Historically, women and girls have been called "hemophilia carrier". It has been argued that because hemophilia is an

X-linked disorder and therefore mainly affects males, there is a bias toward assuming that hemophilia carriers are asymptomatic (54). However, there is now an increasing body of evidence that women and girls with such a gene variant experience heavy periods, joint damage, pain and impaired quality of life (54–57). It has been argued that this labeling system is an example of sexism and hampers diagnosis, care and research (55,57).

Therefore, a new nomenclature for women and girls with hemophilia has been suggested by the ISTH, which suggests using five categories: women and girls with mild, moderate and severe bleeding, symptomatic carrier and asymptomatic carrier (54). The two "carrier" classifications are intended to describe women and girls with normal coagulation factors, acknowledging that they still may have an increased bleeding tendency. It is also suggested that the term "hemophilia carrier" should be reserved for genetic counselling (54).

These debates show how classifications of disease severity serve various purposes and uses: predicting disease progression, providing access to treatment options, acknowledging impacts on quality of life, and guiding social policies, to name a few. In addition, the discussion highlights how social influences (in the discussion surrounding women and girls with hemophilia) and progress in treatment options (in the discussion surrounding classification of hemophilia severity) have impact on how such concepts are interpreted and used. Lastly, the debate prompts questions about which perspectives should be incorporated in these decisions and who gets to decide on the final definition. For instance, authors in this debate draw attention to the importance of incorporating the views of both adult and child hematologists (50), argue for the importance of ISTH Scientific and Standardization Subcommittee (SSC) in taking the lead on these decisions (50,53), or explicitly highlight their own experience as person living with hemophilia as well as professional expertise (51).

The concepts of health and disease

The questions surrounding classification that are arising now in the field of hemophilia are similar to questions surrounding the definitions of health and disease in other medical fields and debates in the philosophy of medicine. The latter debate has resulted in the development of various theories of health and disease that coexist. Three prominent theories are presented below, as they may inform the discussion surrounding cure for hemophilia.

The biostatistical theory of health

The "biostatistical theory of health" (BST) is one of the most prominent theories on health. Christopher Boorse, a philosopher of medicine, claimed that disease should be defined based upon an assessment of the biological functioning of one or more organs of an organism. According to the BST, disease is "a type of internal state

which is either an impairment of normal functional ability, i.e. a reduction of one or more functional abilities below typical efficiency, or a limitation on functional ability caused by environmental agents". Following from this definition, health "is the absence of disease" (58). In this definition, normal functioning refers to a certain part or organ's contribution to an organism's reproduction or survival. According to Boorse, in order to understand statistically normal functioning, we should examine the functioning of a specific age group of a sex. Importantly, according to the BST, the concepts of health and disease are merely descriptive and do not refer to any values. Boorse has described his definition of disease as corresponding to a pathologist's use of the term rather than a clinician's.

This theory faced several criticisms. In particular, it has been questioned whether the most important goals of an individual are reproduction and survival (59). Furthermore, some have argued that when statistically normal functioning is taken as a reference, "common diseases" that occur in a large part of the population, such as caries, will not be considered a disease (58).

Within the domain of hemophilia, several scholars mention that a cure entails endogenous factor expression, sometimes also referencing the decrease of bleeding symptoms and no further need for prophylaxis (29–32,34,40,42,45,47). These interpretations appear to align with the biostatistical theory of health, equating health with statistically normal functioning.

Holistic theories of health

Holistic theories of health refer not just to survival, but to quality of life as well (60). Such concepts of disease therefore include evaluative judgements. One of the most important developers of such a notion of health is the philosopher Lennart Nordenfelt. He claimed: "A is healthy if, and only if, A has the ability, given standard circumstances, to reach all his or her vital goals" (60). Here, vital goals refer to a person's most important goals in life. The definition of disease follows from the definition of health: "A has a disease if, and only if, A has at least one organ which is involved in such a state or process as tends to reduce the health of A. The disease is identical with the state or process itself" (60). This theory has received criticism as well. "Vital goals" is considered to be too broad and at risk of medicalization when many phenomena may be considered as "ill health" (61).

Some authors mentioning cure for hemophilia refer explicitly to quality-of-life related aspects (6,48) or highlight how a cure can contribute to improving quality of life (18–20). Although our analysis indicates that the term cure is used more regularly to describe improvements in the expression of coagulation factor levels than improvements in quality of life, there has traditionally been much attention for quality-of-life related aspects in hemophilia care. For instance, recently, the concept of a "hemophilia-free mind" has been proposed to guide future research and care

for hemophilia (62–64). This concept refers to the absence of psychological burden and constant thoughts about hemophilia, thereby freeing them from the impacts of hemophilia on their behavior and daily activities (62). From a more holistic perspective on health, this concept could very well be considered as aligning with being cured of hemophilia.

WHO definition and positive health

Recently, general practitioner Machteld Huber has developed a theory of "positive health" (65). Positive health was mainly developed as an alternative to the broad World Health Organization (WHO) definition of health, being "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (66). Because of the requirement of "complete health" in the WHO definition, many people would be regarded unhealthy for a significant part of their life (65). According to the concept of positive health, health should be defined as "the ability to adapt and self-manage in the face of social, physical and emotional challenges" (65). Positive health is intended to be a broad perspective on health, consisting of six dimensions: bodily functions, mental well-being, meaningfulness, quality of life, participation, and daily functioning (67).

From the perspective of positive health, managing aspects of daily life becomes more important and the exact factor levels achieved might become less relevant. This aligns with recent findings from an interview study we conducted, which indicated that some Dutch people living with hemophilia A prefer emicizumab over gene therapy, at least with the current results of gene therapy. They expected to have more freedom with emicizumab and feared that after gene therapy they would be considered to have mild hemophilia, and no longer be allowed to store clotting factor at home to use in case of emergency, thereby limiting their independence (68).

Open questions and considerations for discussion

This article has highlighted several topics that require further consideration in discussions surrounding cure. A first aspect concerns the durability of a cure. As discussed in the section on the characteristics of cure, it is often mentioned that cure implies a single treatment with lasting effects. However, one of the more concrete definitions of cure in an outcome set states that the effects of a cure last for five years after treatment. Such demarcations in time are required in to measure effectiveness in trials, but may be in tension with the (implicit) assumptions surrounding the concept.

Second, two findings of gene therapy trials warrant attention in this regard. To begin, the effects of gene therapy, particularly for hemophilia A, appear to decrease over time (69). If a cure is supposed to be "lifelong" or "durable", as many authors imply, it is thus questionable if gene therapy for hemophilia A lives up to

this promise, even if it may meet the criteria of a cure as set out by a definition with a time-limit of 5 years. Further, many people require immunosuppressive therapy to treat liver enzyme elevations after gene therapy (70). If this additional treatment is required, it is questionable if gene therapy can be considered a "single treatment".

Third, current debates raise the question whether there should be an overarching, agreed-upon definition of cure. It appears that currently, many authors seem to have interpretations of what a cure means, rather than explicit definitions. In a recent paper, we have argued that different cure concepts for gene therapy may coexist, as long as each concept is capable of serving the goals it is supposed to serve in a given context (71). Nonetheless, in the debate on disease classification, there appears to be a desire for one clear, agreed-upon definition. Incorporating the notion of cure in core outcome sets appears to be a move toward a standardized definition of cure. If there is a desire or need to provide an explicit definition of cure, several questions arise. Who should have a say in defining the concept, and for what contexts is the concept developed? And, similar to concerns arising in the discussion surrounding classification of hemophilia, would it be problematic if a definition is used in a context for which it was not developed?

Conclusion

We have shown that the term "cure" is used ambiguously in the field of hemophilia, referring to various potential outcomes. Some of these interpretations appear to be mainly focused on normalization of clotting factor levels and bleeding symptoms, whereas others adopt a broader perspective incorporating quality of life. Similarly, whereas many interpretations focus on the long-lasting effects of cure, some incorporate a (limited) 5-year durability in the definition of cure. Further, we have shown how the discussions surrounding classification of hemophilia and the concepts of health and disease relate to the discussion on cure. This review thereby raises the question whether there should be one or more explicit definition(s) of cure, and if so, whose perspectives and opinions should be involved in developing this definition.

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CHAPTER 7

General discussion

Contribution of the author of this dissertation:
Designed and wrote the chapter; revised based on feedback from supervisory team.

After several decades of research, the first gene therapy products for hemophilia A and B received market authorization by the EMA and the FDA during the years in which the research for this thesis was conducted. Apart from the great promises of gene therapy and its first successes, gene therapy also raises several ethical issues. This thesis aimed to evaluate how gene therapy can be further developed and integrated into clinical practice in an ethically responsible manner, responsive to the needs of key stakeholders. To reach this goal, two main research questions were formulated: 1) What are the ethical aspects of hemophilia gene therapy? And 2) What does it mean to cure hemophilia? In this final chapter, I answer the main research questions of this thesis and reflect upon the findings and methods of the study, ending with recommendations for practice and further research.

Main findings

Question 1: What are the ethical aspects of hemophilia gene therapy?

The first research question concerns the identification of ethically relevant aspects of hemophilia gene therapy. This was mainly done through a literature review as described in chapter 2 and an interview study with stakeholders, which is described in chapter 3. Each of these chapters provides an overview of several ethical themes. In addition, the analysis of cure in the later chapters contributes to identifying ethical aspects as well. By integrating these findings, three overarching ethical aspects of the research and clinical application of gene therapy for hemophilia can be identified.

Potential to live up to expectations

Genetic research in general and gene therapy in particular has always elicited great expectations and has been prone to attracting hype (1,2). This is no different for gene therapies for hemophilia. As explained in chapter 2, the literature describes how gene therapy is often framed as being able to circumvent most, if not all, downsides of standard treatment. For instance, much literature published in the 2000's and 2010's mentions how gene therapy is expected to decrease the costs of lifetime treatment for hemophilia, thereby contributing to the goal of increasing global equality in access to treatment; prevent inhibitor development; and forego the need for intravenous administration, thereby reducing the burden of treatment (3–6). This last aspect is said to not only increase overall quality of life for people living with hemophilia, but in particular to improve treatment outcomes and quality of life for people with

limited venous access, such as small children (chapter 2). According to several stakeholders in the field, the expectations and hopes of gene therapy have increased over the years, mainly because of the initially very promising effects observed in gene therapy trials for hemophilia A (chapter 3).

Yet, the gene therapy products currently most advanced in development, including those approved for market access, do not appear to live up to many of these promises. Importantly, current gene therapy products are likely to be inaccessible to several groups of people living with hemophilia who have limited access to treatment or for whom standard treatment is most challenging for a variety of reasons, including children, people with inhibitors and people living in low-resource settings (chapter 2). Furthermore, given the improved standard of care after the introduction of emicizumab, several people living with hemophilia A question the added value of current gene therapy techniques, especially when taking into account the risks and uncertainties associated with gene therapy (chapter 3).

One particularly prominent expectation of gene therapy that has persisted over the years is that it will provide a definitive cure for hemophilia. However, it is often left undefined what is meant with a cure, and a consensus definition of the concept is lacking in the field (chapter 6), thereby leaving this promise rather abstract. Furthermore, some interpretations of cure go beyond what can be offered solely by gene therapy, such as the idea that cure consists of a normalization of life or a change in identity (chapter 5). This combination of factors makes the promise of cure intangible and thereby hard to reach

Independence

For many people living with hemophilia, a wish to increase their independence is an important reason for wanting gene therapy. Many people living with hemophilia feel constrained in their ability to live their life as they want to or to make choices spontaneously, without having to take their hemophilia into account (chapter 3). Several of these individuals indicated how they had to incorporate hemophilia treatment in their daily life and on special occasions, and how hemophilia had influenced certain life decisions, such as their choice of career. They hoped that gene therapy would enable them to live their life more freely. Importantly, many people living with hemophilia A indicated that they had already achieved this goal with emicizumab (chapter 3).

Yet, it also became clear that many people living with hemophilia feared that gene therapy would limit their freedom and increase their dependence on their treatment center (chapter 3). This mainly has to do with the current treatment guidelines and practices in the Netherlands. According to current treatment guidelines, people living with severe hemophilia usually have a stock of clotting factor at home, which they can use when needed. This gives them the freedom to

time their prophylaxis in anticipation of an activity that poses a bleeding risk (such as dental treatment or skiing), or to treat themselves in case of trauma. People living with mild hemophilia, in contrast, are not allowed to store clotting factor at home and are generally not trained to self-infuse. Therefore, people living with mild hemophilia need to contact their treatment center whenever they plan to undertake such an activity or experience an accident. Many of the respondents in the interview study were concerned that after gene therapy, they would no longer be allowed to store clotting factor at home. They feared that this would make them more dependent on their treatment center, thereby limiting their freedom (chapter 3).

In line with these concerns, several health care providers worried that people living with hemophilia would lose the skill of injecting themselves intravenously when no longer having to do this on a regular basis after gene therapy. This was considered to be problematic, as it is likely that they might still need to self-infuse after trauma (chapter 3). Based on these concerns, we concluded in chapter 3 that independence is not solely nor self-evidently increased through gene therapy, as there are multiple factors that influence the extent to which people living with hemophilia can treat themselves without relying on their treatment center and is thus also influenced by policies and treatment guidelines.

In chapter 4 we took a broader look at independence within hemophilia care, by reflecting on patient empowerment and self-management in the context of personal health records. We argued that although personal health records assign additional self-management tasks to their users, these self-management tasks do not necessarily lead to users being able to live their life according to their own wishes, while they do create additional work.

Fair access to gene therapy

Concerns about the costs of gene therapy products and its impact on accessibility came up regularly in the literature (chapter 2) as well as in the interviews we conducted (chapter 3). Already before the first gene therapies for hemophilia reached the market, there were concerns about its expected high price tag, based on the price of gene therapies for other indications, many of which have had the dubious honor of being the most expensive drug in the world (chapter 2). Yet, it was also regularly argued that, given the costs of other hemophilia treatment options, gene therapy would be cost-effective and might even contribute to decreasing the global treatment gap (chapter 2).

There were also concerns that because of the high costs, gene therapy would become inaccessible to people living with hemophilia, as it would not be reimbursed by general health insurance (chapter 3). Although it has never happened before in the Netherlands, some health care providers reflected on a situation in which only some people living with hemophilia would have access to gene therapy, whereby the

decision who would have access was made on the basis of non-medical grounds. These health care professionals indicated that they would not want to be involved in deciding on the distribution of gene therapy based on non-medical criteria (chapter 3).

Question 2: What does it mean to cure hemophilia?

The second research question of this dissertation focused on one of the main promises of gene therapy, to provide a cure for hemophilia. As it is generally ill-defined what a cure means, we set out to explore various interpretations and uses of "cure". In chapter 5, we identified the use of cure in various medical fields and evaluated the different uses of the term in various settings. In chapter 6, we explored how cure is used specifically in relation to hemophilia and related that to various concepts of health and disease (chapter 6).

Within the field of hemophilia, the term "cure" is used regularly in relation to gene therapy, but a definition is seldomly provided. The term is sometimes defined in sets of core outcomes for hemophilia treatment, but these definitions differ (chapter 6). For instance, in some situations cure is defined as lasting at least five years, whereas others state that a treatment has to be effective life-long to be considered a cure. Based on the use of the term, we identified that a cure for hemophilia is often taken to be long-lasting, is considered to lead to continuous endogenous factor expression and in some cases, related to an increase in quality of life (chapter 6).

In other medical fields in which the term is discussed more elaborately, cure can be conceptualized as a "normalization of the body", as "obtaining a normal life" or as a "change in identity" (chapter 5). These different interpretations of the concept can go hand in hand, but there are also situations in which cure is achieved according to one interpretation, but not according to other interpretations. This may create misunderstanding, which may hamper the informed decision-making process of people living with hemophilia or influence the self-image of people living with hemophilia. At the same time, it is not necessarily problematic if there are multiple definitions of cure, as long as each definition serves the appropriate goal in a certain setting, and all stakeholders involved use the same interpretation in that context or are aware of the differing interpretations of others (chapter 5). Therefore, it may not be necessary to define a single definition of cure for hemophilia. However, if such a definition is desired by the field, the field should consider who should be involved in developing the definition (chapter 6).

When comparing chapters 5 and 6, it becomes clear that most interpretations of cure as used in the hemophilia field fit our categorization of cure as "normalization of the body", as they describe bodily functionalities such as normalized clotting factor levels and not having a need for clotting factor replacement therapy. Yet, the other interpretations of cure appear to be relevant for people living with hemophilia as well, potentially even more relevant. As shown in chapter 3, people living with

hemophilia desire gene therapy because they expect it will give them more freedom and independence, which aligns with an interpretation of cure as obtaining a normal life. Further, as shown in chapter 2, some people living with hemophilia are worried that a cure through gene therapy will change their identity.

Widening the lens: Towards the ethically responsible further development and implementation of gene therapy

On the basis of findings of this thesis as well as reflections on the literature, I identify several topics that require further consideration to facilitate the ethically responsible further development of gene therapies, as well as the uptake of gene therapies in clinical practice.

Re-evaluating the rationale for gene therapy

When the first gene therapies for hemophilia were approved by the European Medicines Agency (EMA) and United States Food and Drug Administration (FDA) in 2022 and 2023, the products were admitted to a treatment landscape that was very different from the one existing when gene therapy for hemophilia was first envisioned in the 1970s. These developments call for a re-evaluation of arguments brought forward for the development of gene therapies for hemophilia.

One argument that is often brought forward, which has already been discussed briefly, is that gene therapy will allow to circumvent many of the burdens of standard clotting factor replacement therapy (3,7). The burdens of treatment are experienced differently by different people, as a result of which it is subjective whether gene therapy will improve quality of life more than other treatment options do. Some people living with hemophilia experience the intravenous injections as burdensome, whereas others indicated that they preferred intravenous over subcutaneous injections. For some people with hemophilia A I interviewed, emicizumab had already achieved the goal of a much less burdensome treatment. These respondents also indicated that gene therapy in its current form was not preferable to emicizumab. Other (parents) of people living with hemophilia spoke of the potential benefits of no longer having a need for regular self-infusions, which would be a benefit of gene therapy (chapter 3).

A second argument put forward regularly is that gene therapy will provide a lasting cure with just a single treatment (8–10). However, as is argued in chapter 5, it is unclear what constitutes a cure, as the term is often ill-defined. I argued that multiple interpretations of cure can exist alongside each other, as long as they are suited to the context in which they are used. However, this implies that gene therapy may not reach this goal if people living with hemophilia have a different expectation of cure (for instance, obtaining a normal life) than physicians (for instance, normalization of the body). Further, recent trial results indicate that the effects of gene therapy for

hemophilia A decrease over time (11,12), indicating that the effects might not be as long-lasting as hoped. Last, as also described in the literature review in chapter 2, many people who participated in a gene therapy trial require immunosuppressive therapy to treat elevated liver enzymes (11). For many, this was the hardest part of participation in the trial and some described having to take immunosuppressive therapy as more burdensome than their regular hemophilia prophylaxis (13). The need to use additional medication in order to prevent gene therapy from being rejected by the body makes it, at least for many people, no longer a single treatment.

Third, it is often mentioned that gene therapy is expected to be cost-effective, given the high price of life-long prophylactic treatment (14). Because of this, it is expected that gene therapy will be able to contribute to the World Federation of Hemophilia's goal of "Treatment for all", by being able to provide a therapy for people living with hemophilia living in low-resource settings who currently have no to limited access to treatment (15) Early cost-effectiveness assessments have indicated that gene therapy is likely to be cost-effective, although such analyses are hampered by intransparency surrounding costs of standard treatment and, at the time, no knowledge about the costs of gene therapy (16).

Now that the first gene therapies have reached the market, their high price tag raises discussion. At the time of writing this section, Hemgenix, the first approved gene therapy for hemophilia B, is the most expensive drug in the world with a price tag of $3.5 million for a single treatment (17). The costs of gene therapy are expected to be a major challenge to implementation in low-resource settings (18). The costs of gene therapy have also raised questions about its accessibility in resource-rich settings. For instance, in the Netherlands, it was advised that the product should only be reimbursed after price negotiations. Similarly, in the United Kingdom, Hemgenix at first received a negative pre-advice for being offered in the NHS, given its high price tag, before it received a positive advice.

A further argument brought forward in favor of the development of hemophilia gene therapies is that hemophilia is considered to be the ideal model for validating more general gene therapy principles (11,14). Several reasons have been put forward for this. For instance, hemophilia is a single-gene disorder and the effect of gene therapies, an increase in clotting factor levels, is easily measurable with clotting factor assays (11). Other reasons regularly mentioned are that there is a wide therapeutic window and that a small increase in clotting factor levels (from <1% to >5%) already leads to significant clinical benefit, from severe hemophilia to mild hemophilia (19). However, as presented in chapter 3, several people living with hemophilia, in particular those living with hemophilia A, do not consider a gene therapy that leads to mild hemophilia an improvement compared to their current treatment. They think so because of the risks and uncertainties that still surround gene therapy and the current high standard of care. This seems to indicate that the

aforementioned wide therapeutic window, has shifted. Other treatment options have already achieved a clinical outcome in the moderate to mild range, as a result of which a gene therapy that achieves this outcome has become less attractive. This means that the window of desired outcomes has become narrower; whereas any improvement over 1% was first considered desirable, our interviews indicate that this bar is now raised to an outcome in the normal range, roughly above 50%.

Thus, it appears that many of the arguments used in the discussion surrounding gene therapy need to be modified to be applicable to the current situation or are no longer relevant in the discussion. This does not mean there are no arguments to further pursue gene therapies for hemophilia, as there are still several. To begin, people living with hemophilia B are still dependent on intravenous injections for treatment. Being dependent on clotting factor replacement treatment also means that some people still suffer occasional bleeding. It is expected that gene therapy will lead to more people becoming completely "bleed-free". Moreover, for some people living with hemophilia, no longer having a need to inject treatment, also subcutaneously, brings great benefit.

Furthermore, as identified in chapter 3, for many people living with hemophilia, gene therapy can bring a feeling of freedom and independence. Gene therapy might be able to achieve this goal better than other treatment options. This freedom, however, is not automatically achieved with gene therapy, and depending on the outcomes of gene therapy, people living with hemophilia might grow more dependent on their treatment center. Which of these effects will be achieved does not solely depend on the effectiveness of gene therapy, but is dependent on other factors, such as treatment guidelines and the maintenance of skills to inject intravenously as well.

Becoming a person living with(out) hemophilia

As has been argued, there are several reasons why it is questionable if gene therapy will lead to a cure for hemophilia. The term "cure" is used ambiguously, and the concept of hemophilia appears to be changing as a result of new treatment options. Further, long-term effects of gene therapy are still unknown. There is thus both a conceptual uncertainty and an epistemic uncertainty. As a result of these uncertainties, I will argue, gene therapy might lead to people who are in between a state of health and a state of disease. The state of being in between health and disease has already been described in the literature, both for people who do 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 (20), the second group is described as being "in waiting" after a diagnosis, before the onset of symptoms (21). Gene therapy can, paradoxically, lead to a state in which people living with hemophilia become both "in remission" and "in waiting".

The term "remission society" has been used to describe all people who have had a disease and are effectively well, while at the same time still living with the consequences of the disease (20). According to sociologist and cancer survivor Arthur Frank, who introduced the term remission society, this includes all those with a history of illness. This group consists of, but is certainly not limited to, cancer survivors who are not declared "cured" because the cancer might return (22), 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 (20). When gene therapy for hemophilia reaches the effects that are aimed for in trials (i.e. long-term increase in coagulation factor levels sufficient to forego the need for clotting factor replacement prophylactically or in case of trauma) people will not have any symptoms of hemophilia anymore. However, as hemophilia is a congenital disorder, they will still have to take it into account in reproductive choices, and these people will continue to live with the consequences of hemophilia. This may include joint damage that will continue to progress, potential psychological burdens, as well as any other consequences that have resulted from hemophilia.

Results of gene therapy trials seem to indicate that, at least for most individuals, gene therapy is effective in reducing, or in some cases fully eliminating, the symptoms of hemophilia, with coagulation factor levels raised to the normal range, allowing a life relatively unencumbered by hemophilia. At the same, these effects appear to decrease over time (11). How long the effects remain is, however, hard to predict, as there is still a scarcity of long-term follow-up data and the data that exist indicate that there is much variation between individuals regarding the duration of these effects, as a result of which it is hard to predict if and when they have to return to prophylactic treatment. This puts these people into a position similar to that of "patients-in-waiting".

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, for instance for Alzheimer's disease (21,23). The term is also used to describe people who are at risk for developing disease, such as people with high cholesterol (21). 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.

Of course, people living with hemophilia differ from the groups traditionally described as "in waiting", as they have not only been diagnosed with hemophilia from a young age, but have also experienced its symptoms and have had a need for continuous treatment from the moment they learned to crawl as an infant. Nonetheless, because of the promise and expectation of cure after gene therapy, they share the characteristics of "patient-in-waiting"; after gene therapy they do not experience hemophilia symptoms, but there is a chance that these symptoms will

reoccur after a certain amount of time, while it remains uncertain if and when this will happen. As a result, gene therapy might lead to a group of people who are not best described as living with hemophilia, nor as being free from hemophilia. Instead, a new group arises, people living in between health and disease, with an uncertainty about their future well-being.

Such a state has several ethical consequences. First, people may need to cope with uncertainty and fear for their future health and well-being. The interview study in chapter 3 found 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 when the effects would disappear, and they would need to return to prophylactic therapy. Similar findings have been reported in another qualitative study (13). This type of psychological distress requires attention and appropriate support and care.

Furthermore, this uncertain state raises questions about what medical care is suitable and appropriate for people living in this uncertain state. Part of the reason why people desired to be cured from hemophilia is to be free from doctor's appointments and medical check-ups (chapter 3). Yet, regular check-ups may be desired to monitor how the person is doing and if their clotting factor levels are still sufficiently high. Moreover, participation in monitoring or follow-up research is highly desirable to obtain knowledge about the long-term effects of gene therapy. Continued need for check-ups can also mean that the treatment goal of a "hemophilia-free mind" (24) will not easily be reached.

To a certain extent, reaching this state in between health and disease is inherent to gene therapy; hemophilia will remain a congenital disorder, which can be passed on to future generations, and joint damage that has been incurred before will remain. However, part of this uncertain state may be temporary or merely the result of the current state of the art. For instance, because of the improved standard of care for hemophilia, 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 of gene therapy will increase, we may be able to give a better prediction of 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 hemophilia symptoms.

Treatment goals and defining progress

As was shown in chapter 6, the progress in treatment options for hemophilia and its resulting enhancement of quality of life, have led to a discussion regarding the (suitability) of the classification of hemophilia into the categories severe, moderate and mild. Whereas this understanding of hemophilia severities used to be relatively

straightforward, based on the measurement of coagulation factor levels, it is now becoming increasingly opaque. It is not uncommon for new biomedical technologies to change disease definitions or concepts (25). It is therefore likely that a technology such as gene therapy, which has the potential to make an even bigger change to the standard of care, will elicit such impacts as well.

In particular, it can be hypothesized that gene therapy will increase the threshold for defining a cure for hemophilia. The developments in the last decade have already started to do so. For instance, the improved treatment outcomes of emicizumab have shed light on a relatively new symptom: joint microbleeds (26). It is not certain if joint microbleeds exist, but several people living with hemophilia report improvements in their joint functioning after starting emicizumab, which is hypothesized to be because of the achievement of continuously higher factor levels, which are thought to be protective against microbleeds (26). These microbleeds are suspected to have always been subclinical, but to have become apparent because of the overall decrease in bleeding episodes and improvement in joint health (26). It is not unlikely that these microbleeds, a previously unknown problem, will become a new treatment target, thereby raising the bar for what is asked of a new treatment modality.

This implies that, paradoxically, treatment options that aim to 'cure' hemophilia seem to expand the underlying concept of hemophilia as a disorder and thereby raise the bar for what is considered to be a cure. Although several interpretations of cure were identified in chapter 5, all have in common that they describe a transition from a state of disease or disability to a state without that disease or disability. Thereby, when treatment modalities that promise a cure for hemophilia in reality expand the disease concept, they paradoxically raise the bar for a cure.

By re-defining the disease concept of hemophilia, technical progress in treatment options does not solely provide more effective means of reaching previously established treatment goals but also changes the goals of treatment (25). This effect may be enhanced by the unclarity of the meaning of "cure". Because cure can refer to many different things, the actual goals remain implicit and can relatively easily be replaced by other implicit goals that can also be covered by the concept of "cure".

This (potential) change in treatment goals requires reflection and deliberation. Are the goals desirable, and if yes, for whom? Whose voices have been included and whose have not in the establishment of new goals? Within the field, several outcome sets for hemophilia treatment have been defined by multi-stakeholder collaborations. When such efforts are undertaken in the future, they should take these implicit changes in treatment goals into account.

A change in treatment goals also raises questions about when medical intervention is appropriate, and if it is, what type of intervention is appropriate. A change in the definition of hemophilia might impact judgements about treatment

options. These questions are particularly relevant because the analysis in chapter 5 shows that several of the interpretations of cure are influenced by non-medical factors, such as the opportunities someone has in their life and their narrative identity. It should therefore be critically evaluated what care and efforts to improve the quality of life of people living with hemophilia should happen inside the medical realm, and which should happen outside of that, for instance in the social domain. In line with these considerations, both the enhanced standard of care and a potential change in treatment goals raise questions about priority setting in health research; what should (medical) research focus on, and what is the standard of care to which new treatment modalities should be compared?

Unclear concepts and unrealistic expectations

Because of its great promises, gene therapy for hemophilia is compared to a "holy grail" in several publications (27,28). Similarly enthusiastic portrayals of gene therapy can be recognized in news media when reporting on the results of trials. For instance, in July 2022, the BBC headlined an article with the title "Transformational therapy cures hemophilia B" (29), when describing the results of a phase 1/2 trial. In the article, a person living with hemophilia who participated in the trial speaks of "miraculous results". In 2017, the results of a trial for hemophilia A were described as "mind-blowing" by the BBC (30). Similarly, the Dutch newspaper "Algemeen Dagblad" headlined "Curing clotting disorders with an injection once every ten years" in 2022 when reporting on a company about to start clinical trials (31). This type of rhetoric seems to be used when reporting on trials of innovative treatments for all kinds of disorders. For instance, in early 2024, Dutch newspaper de Volkskrant cites physicians who speak of having "goosebumps", when describing the results of a trial in which the first Dutch people have received a CRISPR-Cas9 intervention for hereditary angioedema (32).

In such narratives, a hype surrounding gene therapies can clearly be recognized. Hype about new technologies is usually defined as either an overestimation of the significance or benefits of a technology, thereby overlooking its risks, or giving unrealistic timelines for the expected application of a technology (33). Hype is a frequently occurring phenomenon with regard to genetic technologies (2). Given that these news items use hyperbolic language and speak of having obtained a cure based on the results of data from phase 1/2 trials, which mainly aim to assess safety and only assess efficacy as a secondary goal, such phrasings can be categorized as being part of contributing to hype. Similarly, in the academic literature, predictions regarding the timeframe for the arrival of gene therapy have not materialized (34). Because hype arises from an overestimation of benefits, it can be hypothesized that the opacity surrounding the meaning of "cure" contributes to ongoing hype, as it leads to a situation in which there is always a new imagined outcome on the horizon.

It has been argued that hype is a normal stage of technological development, and that promissory narratives are required to secure resources and funding for conducting research (33,35). Yet, hype also has ethically undesirable consequences: it may lead to therapeutic misestimation, it may lead to erosion of public trust in science; it may lead to invest resources in certain technologies at the expense of other technologies or treatment options; and it could lead to a premature translation to the clinic (33). Therefore, as argued in chapter 5, it is important to avoid excessive use of the term "cure".

Recognizing the importance of questions surrounding identity

At the start of this PhD trajectory, there were concerns in the field that gene therapy might impact the identity of people living with hemophilia. This was mainly based on a publication in The Atlantic, in which a person living with hemophilia was interviewed who indicated that he does not want to be cured of his hemophilia, as the disorder is a part of his identity (36). As he is quoted in the article: "I am hemophilia. I don't have it. I am hemophilia. So when they come to me and say, 'We've got a genetic cure for hemophilia,' to me, that's just as weird as if you said you've got a genetic cure on the horizon for your left foot. This is really who I am" (36). This publication appears to have caused concern in the field about the desirability of gene therapy, although empirical research on this topic was, and still is, minimal. A few years later, a focus group study was published that also found indications that some people living with hemophilia felt their identity might be negatively impacted by gene therapy (37). As discussed in chapter 2, in the literature, this has mainly been interpreted in light of the "burden of normality" (38).

In the interview study in chapter 3, we found no indications that people living with hemophilia anticipate an (undesirable) change in identity resulting from gene therapy, although there were indications that hemophilia had impacted the identity of people living with hemophilia, by shaping several choices in their life and having a social network with other people living with hemophilia. This impact of hemophilia on identity (development) is also supported by other qualitative research (39,40). Further, in chapter 3, we suggested that rather than understanding this fear for a change in identity as a "burden of normality", it can also be understood as a fear of no longer belonging to a group of people with a certain condition, comparable to discussions in the field of disability studies.

The empirical findings of a potential change in identity do not provide much clarity yet, and it is uncertain how they should be interpreted. Nonetheless, the issue should not be overlooked, as the uncertainty surrounding the problem may in part be constituted by a conceptual unclarity. It appears there are several different interpretations of the term "identity", which vary both in and between disciplines, as well as between academic definitions and folk understandings of

the term. For instance, while I conducted the interviews, it became clear that it is challenging to ask about potential changes in identity, as the concept appeared to have a different meaning for different people. For instance, some participants responded by saying they "didn't care for identity politics", or by asking me if gene therapy also impacts the genes that determine your personality – because why else would it impact your identity? These responses represent different connotations people have with the term. Further, although they did not relate these anecdotes to the term 'identity', participants related stories about how hemophilia had shaped their choices surrounding education, career, place of residence and holiday plans, amongst others, and how they had gained social relations and friendships via the hemophilia community.

Similarly, in the field of philosophy, research surrounding identity has focused on the reidentification question (what makes that a person at a certain point in time can be reidentified as the same person at a different point in time?) as well as the characterization question (when are certain psychological characteristics and experiences properly attributed to a person?). Multiple theories have been formulated in response to each of these questions (41). Further, in fields such as bioethics, sociology of health and medical anthropology, there has been considerable debate regarding identity change or identity crisis in response to various medical treatments, such as gene or cell therapies, organ transplantation, cochlear implants and deep brain stimulation (38,42,43). These discussions appear to have led to a wide spectrum of discussions and interpretations of identity. To further complicate matters, the term is sometimes also conflated with related concepts, such as agency, autonomy, personality or the self (44).

This plurality of interpretations and potential misunderstandings can pose challenges to researching the impact of gene therapy (or any other intervention) on personal identity. Yet, the impacts of innovative treatment options on identity (and related concepts) are ethically relevant, as they can influence the desirability of certain therapies, or, as argued in chapter 5, be a form of being cured from hemophilia. The notion of identity is thus ethically relevant and new technological developments may have an impact on the identity of people living with hemophilia. It is therefore important to avoid tunnel vision when assessing and evaluating potential changes in identity arising from gene therapy and/or from curing hemophilia, as it can easily lead to a situation in which phenomena are overlooked or misinterpreted.

Reflections on approach and method

Ethics parallel research

This study adopted ethics parallel research as an approach to study the ethical aspects of hemophilia gene therapy. Ethics parallel research combines several elements in order to study the ethics of emerging technologies: disentangling wicked problems;

upstream or midstream analysis; ethics from within; empirical research; participatory research; and attention to both hard and soft societal impacts (45). These elements are partly overlapping and can be combined in various settings. In this dissertation, I used the elements empirical research, participatory design and the attention to both hard and soft impacts.

To enable ethics parallel research, this study was part of the Symphony consortium. Although no gene therapy was developed in this consortium, the physician-researchers involved in gene therapy trials in the Netherlands were involved in the consortium. At the time of this research project, several gene therapy products had already been tested in trials in the Netherlands. Further, because of the "elastic" nature of the concept of gene therapy, the different phases of technology development along which ethical study can take place overlap (46). Therefore, this dissertation did not focus on the ethical aspects of a specific technological artefact and its development process, such as a specific gene therapy, but has instead focused on the program of gene therapy development for hemophilia.

This leads to a slightly different perspective on the ethics of gene therapy. In policy and ethics discussions, new biotechnologies can be framed as a product, a process, or a program (1,47). The term product describes the artefact and its specifics, such as the mechanisms through which it functions, the techniques and strategies, and the target of the drug. It is generally what we think of when we begin describing gene therapy, and it is also the focus of my description of gene therapy in the beginning of this thesis (1,47). The term process refers to the various actors involved, the oversight and regulatory mechanisms in place, and the geographical location of the research and development (1,47). The program of gene therapy describes what it aims to achieve and the overarching goals to which the research is directed (1,47).

This thesis did so by investing one of the main promises of gene therapy: to provide a cure. This conceptual investigation contributes a new perspective to the ethical debate, which had thus far mostly focused on product safety and informed consent (1). Thereby, this thesis critically scrutinizes the quality of the promises of gene therapy, an important step in ethical analysis (48).

Active involvement of patient representatives

Part of the approach of this research was active involvement of patient representatives. This involvement was initiated and organized through the Symphony consortium of which this study was a part. A patient representative from the NVHP (the Dutch association for everyone with a heritable clotting disorder) participated as a co-author of chapters 3 and 4. They were involved in all stages of the interview study, from research design to writing and publication. Thereby, they had the role of a partner in the research, as defined by the Involvement Matrix (49). In addition, the topic list for the interviews was sent to the panel of patient representatives within

the consortium for comments and suggestions. This led to the inclusion of additional topics in the list. This panel had the role of co-thinker in the research project (49).

The involvement of patient representatives impacted the research in several ways. First, as already mentioned, the involvement of patient representatives led to the inclusion of additional themes in the topics for the interviews. These topics were not found in the literature study, but were considered relevant to people living with hemophilia. For instance, patient representatives brought forward that it might be considered undesirable that current gene therapies do not prevent hemophilia from being passed on to future generations. This aspect is often considered to be beneficial in ethical literature, as germline modification is generally considered to be more ethically contentious than somatic gene therapy. Furthermore, because of their role within the patient society, the patient representatives contributed knowledge regarding the development and mechanisms of gene therapy, the expected timelines surrounding EMA approval and other regulatory aspects surrounding hemophilia treatments.

The participation of patient representatives – both in the interview study specifically and in the Symphony consortium more broadly – also had instrumental value in the recruitment process of the interview study. Because of the contact with the NVHP, I was able to send out an invitation to participate (along with reminders) through their newsletter and social media. Additionally, I occasionally sought participants with highly specific characteristics for the interviews, such as people who underwent a liver transplantation. Patient representatives helped identify and reach out to people who met these criteria, as did some nurses and physicians with whom I was in contact. Furthermore, on occasions when I was invited to present at an event of the NVHP and join the drinks afterwards, informal conversations often led to people asking about my research. Many offered to share information about my study with a family member or friend living with hemophilia who was not involved in the NVHP, helping to increase the diversity of participants in my sample.

Being invited to meetings for people living with hemophilia, along with the informal discussions over coffee, helped me reflect on my research and consider any future research I may conduct. Hearing how people talk about their lives with hemophilia gave me a better understanding of what hemophilia entails. More specifically, it was these conversations that made me notice how people discuss the concept of "cure," which eventually led to papers on the topic. I noticed that this term was frequently used without being clearly defined in how people living with hemophilia and healthcare professionals spoke about it, both during presentations and informal conversations, before I noticed the same pattern in the academic literature. Finally, after the interview study had already been published, a patient representative shared with me that one of the participants in the validation meeting had approached them with a question. Apparently, they did not understand what was

expected of them or how they should behave toward the researchers, and they did not feel comfortable asking me directly. From this anecdote, I learned that despite having explicitly stated both in conversation and via email that participants should feel free to ask any questions, my position as a researcher had made them hesitant to approach me.

Concluding remarks and recommendations

Much has changed since the days in which European royals died after a minor incident, as a result of their hemophilia. The field has now reached a state in which people living with hemophilia do not only have a near normal life expectancy, but also a growing array of treatment options to choose from, allowing their quality of life to increase. Having just entered the market, gene therapy is now becoming one of those treatment options. Gene therapy for hemophilia has always been considered a prime test case for general gene therapy development. It can now also be used as an example of how a treatment can, on the one hand, have several benefits for patients, yet on the other hand still fail to live up to expectations. Hemophilia gene therapy can therefore be used as a test case for toning down expectations of a highly anticipated treatment. Below, I provide several recommendations for the further ethically responsible development of gene therapy and its uptake in clinical care.

Design care for hemophilia to enhance independence

As this research has shown, for many people living with hemophilia in the Netherlands, one of the most important reasons for desiring gene therapy is its potential to provide them with more independence and the ability to live their life free from restrictions posed by hemophilia and its treatment. However, this goal is not necessarily achieved by gene therapy – gene therapy can even work counterproductive – and cannot solely be achieved by gene therapy or other innovative treatment options. When adopting gene therapy in clinical practice, a process that is beginning now, it is important to keep patient preferences in mind, and to avoid the assumption that gene therapy will automatically achieve these desired outcomes, as a 'technological fix'.

Instead, to achieve this goal, the entire care process needs to be designed in a way that facilitates independence for those people living with hemophilia who desire this. This can include (amongst others) eHealth tools such as a personal health record, the frequency of medical check-ups, both with and without gene therapy, and rules regarding a home supply of clotting factor. All these factors together impact the extent to which people can live with a "hemophilia-free mind" (24). Therefore, both hemophilia care and research should focus on ways to foster this independence, and other ways of supporting people living with hemophilia to live a life according to their own wishes.

Reflection on the goals of gene therapy

In addition to critically evaluating to what extent gene therapy allows to reach the goals of cure and independence, there should be attention for any other goals that stakeholders hope to achieve with gene therapy, and how these may change. It appears that the goals of gene therapy for hemophilia have already shifted over time. Therefore, it is important to reflect on the goals that the development of gene therapy aims to achieve, and to evaluate whether they align with the needs of people living with hemophilia.

Attention to the ethics of communicating

As mentioned before, hype surrounding gene therapy is ethically consequential, as it can pose challenges to informed consent and provide misguided direction in resource allocation decisions. The combination of these aspects also poses challenges to informed consent. This means that the current discourse surrounding gene therapy, framing it mainly as a potential cure, is inappropriate and might create false expectations for people living with hemophilia. Instead, a new vocabulary might be required in order to properly capture the experience of living a life after gene therapy.

This hype is, however, created by various actors. This means that not just gene therapy researchers, but also physicians, nurses, people living with hemophilia, patient representatives and the media should take responsibility for the accurate description of gene therapy and its potential.

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APPENDICES

English summary
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English summary

Ever since the first research on gene therapy started in the 1990s, people living with hemophilia and their health care providers have had high hopes that, eventually, gene therapy will be able to provide a cure for hemophilia. People living with hemophilia have a deficiency of clotting factor VIII (hemophilia A) or clotting factor IX (hemophilia B), as a result of which they suffer from spontaneous or trauma-induced bleeding into muscles and joints. The symptoms of hemophilia can be controlled with clotting factor replacement therapy, which requires regular (ranging from three times per week to once every two weeks) self-infused intravenous injections with clotting factor replacement therapy, or the non-replacement therapy emicizumab, which requires subcutaneous injections. Because of this variety of available treatment options, people living with hemophilia in the Netherlands have a life expectancy comparable to that of the general population and increasingly high levels of socio-economic participation and quality of life.

Next to these treatment options, the first gene therapy products for hemophilia reached the market in 2022 and 2023, and more are under development. Gene therapies do not only offer hope for improved treatment and potentially a cure, but also raise several ethical issues. Thus far, most ethics research surrounding somatic gene therapy has focused on research ethical questions, such as questions surrounding participant selection and how to deal with uncertainty. However, as gene therapy is now transitioning from being an investigational product to a product that is part of the treatment palette in clinical practice, different ethical questions become relevant. Furthermore, new biomedical technologies such as gene therapy often change underlying concepts and definitions of disease, which may impact both the desirability of the technology and the goals of medicine. Therefore, this thesis aimed to evaluate how gene therapy for hemophilia can be further developed and implemented in clinical practice in an ethically responsible manner, responsive to the needs of key stakeholders. To this end, two research questions were identified: 1) what are the ethically relevant aspects of gene therapy for hemophilia? And 2) What does it mean to cure hemophilia?

In order to identify ethically relevant aspects of gene therapy for hemophilia, a narrative review of the literature was conducted, which is presented in chapter 2. We identified three ethical themes: living up to expectations; psychosocial impacts; and costs and access. The theme living up to expectations describes the high hopes and expectations surrounding gene therapy, and the challenges that exist in meeting them. In the literature, it is often described that people living with hemophilia hope that gene therapy will provide a permanent cure for hemophilia and that it will prevent many of the downsides of the current standard of care, factor replacement therapy. This includes downsides such as the impact on quality of life, the high costs of treatment and the risk of inhibitor formation, which decreases the effectiveness of treatment. However, this theme also describes how gene therapy has thus far largely failed to live up to these promises, while new risks and burdens have also emerged during the trials. For instance, research shows that many trial participants had to use immunosuppressive therapy, which they considered the worst part of their trial experience. In the theme psychosocial impacts, we discuss current debates surrounding the possibility that gene therapy will impact the identity of people living with hemophilia and the need for psychosocial support. This psychosocial support is required when gene therapy proves to be a cure, since people may need help to adjust to this new situation, as well as when the effectiveness of gene therapy decreases over time, to cope with the uncertainty. 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. Further, we conclude that there is a need to reevaluate the desirability of gene therapy for hemophilia, given the existing uncertainties and the availability of other treatments.

Further ethical aspects were identified in chapter 3, which presents an interview study conducted to obtain insight into stakeholders' morally reasoned opinions on gene therapy for hemophilia. To achieve this, we conducted semi-structured interviews with Dutch people living with hemophilia (n=13), parents of children living with hemophilia (n=5), physicians (n=4), nurses (n=3), a regulator (n=1) and an employee of a pharmaceutical company (n=1). In this study we also identified three themes: freedom and independence; trust and altruism; and incremental benefits. The theme freedom and independence describes the hope people living with hemophilia have of increasing their freedom and independence through gene therapy. They hope that gene therapy will diminish the restrictions they currently experience regarding choice of career, hobbies, or holiday destinations, amongst others. However, we also identified concerns surrounding this increased independence. Several people living with hemophilia fear that when gene therapy turns their severe hemophilia into mild hemophilia, they will no longer be allowed

to store clotting factor at home and/or will lose the ability to self-infuse with clotting factor in case of a bleeding incident, due to which they would become more dependent on their treatment center. Additionally, several health care providers feared that people living with hemophilia will become "reckless" after gene therapy, by responding inadequately in case of a bleed, thereby risking joint damage. The theme trust and altruism describes how people living with hemophilia have a high level of trust in their physician and treatment center as well as in scientific research. Because of this trust, they are willing to participate in trials to help other people living with hemophilia. The theme incremental benefits describes the doubts respondents have about the added value of gene therapy compared to standard treatment. They indicated that the standard of care is already good, and that it is questionable if gene therapy can trump this, given the associated risks and uncertainties. The results indicate that one of the main reasons for which people living with hemophilia desire gene therapy is to become more independent. This cannot solely be achieved through gene therapy, but is also influenced by the policies and practices into which the treatment becomes embedded. We conclude that stakeholders embrace the theoretical potential of gene therapy, while several people living with hemophilia question the added value of gene therapy compared to other treatment options.

In chapter 4, we took a broader perspective on hemophilia care, by evaluating self-management by people living with hemophilia through the use of personal health records. Where chapter 3 identified that people living with hemophilia desire more autonomy, the personal health record promises to increase the autonomy and self-management of its users. In this chapter, we critically evaluate the promises and assumptions of the personal health record, and argue that it appears that personal health records aim to increase both concordant and compliant self-management, while these forms of self-management do not necessarily go hand in hand. Further, we argue that because there are several skills required to work with personal health records, they may be inaccessible to some, thereby risking exacerbating existing health inequalities. We conclude by making recommendations for design scenarios for the further development of the personal health record.

Chapters 5 and 6 focus on the meaning of "cure", as cure is one of the main promises of gene therapy and an important reason for which gene therapy is desired by people living with hemophilia. In chapter 5 we evaluated the promise of cure through gene therapy, by first obtaining better insight into what is meant with the concept "cure". We conducted a conceptual role analysis, examining how cure is used in four different medical fields where the concept raises discussion. We show that cure can be used in three different ways: cure as normalization of the body, cure as obtaining a normal life, or cure as a change in identity. As we consider cure to be a practical term, in line with recent pragmatist contributions to the philosophy of health and disease, multiple interpretations of the concept can exist alongside each

other, as long as each interpretation is context-specific and each of the uses is suitable to the function the notion of cure plays in a certain setting. We end by highlighting three different settings in the domain of hemophilia gene therapy in which the term cure is used and explore the function(s) it serves in each of these settings: the clinical application of gene therapy, in resource allocation decisions for health care, and in decisions on research funding. We conclude that in the clinical application of gene therapy, it would be better to abandon the term cure, whereas a more modest and specified definition of cure, which avoids hype, is required in the context of health resource allocation decisions and decisions on research funding.

Chapter 6 starts with a review of the use of cure in the field of hemophilia. We show that the most explicit interpretations of cure can be found in so-called "core outcome sets" for hemophilia treatment, in which cure is defined as one of the core treatment outcomes. The various definitions of cure in these sets do not always align. For instance, whereas cure is defined as lasting for at least 5 years in one outcomes set, it is defined as a life-long effect in another set. In addition, although it remains seldomly defined, the term "cure" is used regularly. Based on how cure is used in publications, we identified several characteristics of cure: it is a single treatment, the effects are long-lasting, a cure leads to endogenous factor expression, and has a positive impact on quality of life. We then relate the discussion on cure to debates surrounding the classification of hemophilia as well as philosophical debates on the concepts of health and disease. We conclude that the field should be cautious for potential misinterpretation that might arise when using "cure" and critically evaluate when the use of the term is appropriate or not.

In the final chapter, the General Discussion, I return to the main research questions and provide several recommendations for the further responsible development and uptake of gene therapy for hemophilia. I conclude that there are three overarching ethical themes. The first concerns the potential to live up to expectations. It is generally expected that gene therapy will become a cure and circumvent many of the downsides of standard clotting factor replacement therapy. It remains uncertain, however, if these goals can be reached. The second ethical theme is independence. For many people living with hemophilia, the hope of living a more independent life with more freedom was the most important motivation for desiring gene therapy. However, it is questionable if gene therapy will be able to reach this goal, as achieving this outcome also depends on other factors, such as policy. Third, because of the price tag associated with gene therapy, there are concerns about its accessibility and how it can be distributed fairly. With regard to the second research question, this research has shown that "cure" can refer to various different outcomes. These outcomes may be achieved by gene therapy, but they will not automatically be reached.

I argue that several topics require further attention when continuing the development and implementation of gene therapy in an ethically responsible manner. To begin, the rationale for developing gene therapy should be evaluated. Both the standard of care for hemophilia and the state of the art of gene therapy have progressed over the years, as a result of which several of the arguments in favor of the development of gene therapy have changed or might not be applicable anymore. Second, it is important to be aware that after gene therapy, even if it is as effective as hoped, people living with hemophilia may come to occupy a state in between health and disease, in which they are both "in remission" and "in waiting". This may affect the desirability of gene therapy for hemophilia. Third, the progress in treatment options for hemophilia may cause a change in the treatment goals of hemophilia. Therefore, it is important to reflect on a potential change and evaluate what is considered progress in research and treatment for hemophilia. Fourth, the change in treatment goals and the unclarity surrounding the meaning of cure might exacerbate hype surrounding gene therapy. Finally, although there is currently few empirical data about a potential change in identity that may result from gene therapy, this may be the result of various interpretations of the meaning of a (change in) identity. It is thus a topic that still requires further research.

Further, I reflect on the approach of this thesis and how the research process has benefited from active patient participation. I end with three concrete recommendations for the further development of gene therapy and hemophilia care in general: to reflect on the goals of gene therapy, to have attention for the ethics of communicating about gene therapy and to design care for hemophilia in a way that can enhance the independence of people living with hemophilia.

Nederlandse samenvatting

Sinds het onderzoek naar gentherapie begon in de jaren negentig, hebben zowel mensen met hemofilie als hun zorgverleners de hoge verwachting dat gentherapie uiteindelijk in staat zal zijn hemofilie te genezen. Mensen met hemofilie hebben een tekort aan stollingsfactor VIII (hemofilie A) of stollingsfactor IX (hemofilie B), waardoor ze last hebben van spontane bloedingen en bloedingen als gevolg van trauma, met name in spieren en gewrichten. De symptomen van hemofilie kunnen beheerst worden door verschillende behandelopties. Bij factortherapie dienen mensen met hemofilie zichzelf regelmatig (enkele keren per week) intraveneuze injecties met (recombinant) stollingsfactor toe. Daarnaast is er sinds enkele jaren de niet-vervangende therapie emicizumab beschikbaar voor hemofilie A, waarbij mensen zichzelf subcutane injecties toedienen. Dankzij de beschikbaarheid van deze behandelopties hebben mensen met hemofilie in Nederland een levensverwachting die vergelijkbaar is met die van de algemene bevolking en genieten ze een steeds hogere mate van sociaaleconomische participatie en kwaliteit van leven.

Naast deze behandelopties kwamen in 2022 en 2023 de eerste gentherapieproducten voor hemofilie op de markt en er zijn meer producten in ontwikkeling. Gentherapieën bieden niet alleen hoop op betere behandelingsopties en mogelijk genezing, maar roepen ook verschillende ethische vragen op. Tot nu toe heeft het meeste ethische onderzoek rond somatische gentherapie zich gericht op onderzoeksethische kwesties, zoals de selectie van onderzoeksdeelnemers en het omgaan met onzekerheid. Nu gentherapie de overstap maakt van de onderzoekssetting naar een van de behandelopties in de klinische praktijk, komen andere ethische vragen aan de orde. Bovendien veranderen nieuwe biomedische technologieën zoals gentherapie vaak de onderliggende concepten en definities van ziekte, wat invloed kan hebben op zowel de wenselijkheid van de technologie als de behandeldoelen. Daarom is in dit proefschrift gepoogd te evalueren hoe gentherapie voor hemofilie op een ethisch verantwoorde manier verder kan worden ontwikkeld en geïmplementeerd kan worden in de klinische praktijk, met aandacht voor de behoeften van stakeholders. Daartoe zijn twee onderzoeksvragen geformuleerd: 1) Wat zijn de ethisch relevante aspecten van gentherapie voor hemofilie? en 2) Wat betekent het om hemofilie te genezen?

Om de ethisch relevante aspecten van gentherapie voor hemofilie te identificeren, is een narratieve literatuurreview uitgevoerd (hoofdstuk 2). We hebben drie ethische thema's geïdentificeerd: voldoen aan verwachtingen, psychosociale aspecten en kosten en toegankelijkheid. Het thema 'voldoen aan verwachtingen' beschrijft de hoge verwachtingen van gentherapie en hoe complex het is om daaraan te voldoen. In de literatuur wordt vaak aangegeven dat mensen met hemofilie hopen dat gentherapie een permanente genezing zal bieden en dat het veel van de nadelen van de huidige standaardbehandeling, factortherapie, zal verhelpen.

Dit omvat nadelen zoals de impact op de kwaliteit van leven, de hoge kosten van de behandeling en het risico op de vorming van remmers, die de effectiviteit van de behandeling verminderen. Onder dit thema wordt echter ook besproken hoe gentherapie tot nu toe grotendeels niet aan deze verwachtingen heeft kunnen voldoen, terwijl nieuwe risico's en belasting naar voren zijn gekomen in de trials. Zo hebben veel trialdeelnemers bijvoorbeeld immunosuppressieve therapie moeten gebruiken, wat zij als het meest belastende onderdeel van hun deelname aan de trial beschouwen. Het thema 'psychosociale gevolgen' bespreekt de huidige discussies over de mogelijke invloed van gentherapie op de identiteit van mensen die leven met hemofilie en de behoefte aan psychosociale ondersteuning. Deze ondersteuning is zowel nodig als gentherapie genezend blijkt te zijn, als wanneer dat niet het geval is. Als gentherapie genezend blijkt te zijn, hebben mensen mogelijk hulp nodig om zich aan deze nieuwe situatie aan te passen. Als de effectiviteit van gentherapie na verloop van tijd afneemt, kan ondersteuning nodig zijn om met deze onzekerheid om te gaan. Het thema 'kosten en toegankelijkheid' bespreekt de verwachte kosteneffectiviteit van gentherapie en de implicaties daarvan voor de wereldwijde toegankelijkheid van gentherapie. We concluderen dat het nodig kan zijn om het narratief rondom gentherapie te veranderen, van een belofte van genezing naar een van meerdere behandelopties die tijdelijk symptomen verlichten. Daarnaast concluderen we dat het noodzakelijk is om te evalueren hoe wenselijk gentherapie is voor mensen die leven met hemofilie, gezien de bestaande onzekerheden en de beschikbaarheid van andere behandelopties.

In hoofdstuk 3 worden meer ethische aspecten geïdentificeerd, op basis van een interviewonderzoek met als doel inzicht te krijgen in de mening van stakeholders over gentherapie voor hemofilie. Hiervoor zijn semigestructureerde interviews gehouden met Nederlandse mensen die leven met hemofilie (n=13), ouders van kinderen met hemofilie (n=5), artsen (n=4), verpleegkundigen (n=3), een beleidsmedewerker (n=1) en een medewerker van een farmaceutisch bedrijf (n=1). Ook in dit onderzoek zijn drie thema's geïdentificeerd: vrijheid en onafhankelijkheid, vertrouwen en altruïsme, en incrementele voordelen. Het thema vrijheid en onafhankelijkheid beschrijft de hoop van mensen die leven met hemofilie om meer vrijheid en onafhankelijkheid te verkrijgen. Ze hopen dat gentherapie de beperkingen die ze nu ervaren, bijvoorbeeld in de keuze van carrière, hobby's en vakanties, zal verminderen. Uit het onderzoek bleek echter ook dat deze vergrote onafhankelijkheid nieuwe zorgen met zich meebrengt. Verscheidene mensen die leven met hemofilie zijn bang dat wanneer hun ernstige hemofilie door gentherapie verandert in een mildere vorm, ze geen stollingsfactor meer thuis mogen bewaren en/of de vaardigheid verliezen om zichzelf stollingsfactor toe te dienen bij een bloeding, waardoor ze juist afhankelijker worden van hun behandelcentrum. Daarnaast waren meerdere zorgverleners bang dat mensen na gentherapie "roekeloos" zouden

worden en niet adequaat zouden reageren bij een bloeding, waardoor ze het risico op gewrichtsschade zouden vergroten. Het thema vertrouwen en altruïsme beschrijft hoe mensen die leven met hemofilie een groot vertrouwen hebben in hun artsen en behandelcentrum, evenals in de wetenschap. Vanwege dit vertrouwen zijn ze zeer bereid om deel te nemen aan onderzoeken om anderen met hemofilie te helpen. Het thema incrementele voordelen beschrijft de twijfels van respondenten over de toegevoegde waarde van gentherapie ten opzichte van de standaardbehandeling. Zij gaven aan dat de standaardbehandeling al goed is en dat het de vraag is of gentherapie deze kan overtreffen, gezien de risico's en onzekerheden die ermee gepaard gaan. Uit de resultaten blijkt dat onafhankelijkheid een van de belangrijkste redenen is waarom mensen gentherapie wensen. Het is echter niet altijd mogelijk om dit te bereiken met enkel gentherapie, aangezien beleid en de praktijk waarin de zorg is ingebed ook invloed hebben. We concluderen dat stakeholders het theoretisch potentieel van gentherapie omarmen, terwijl verschillende mensen met hemofilie vraagtekens zetten bij de toegevoegde waarde van de huidige gentherapie in vergelijking met andere behandelopties.

Hoofdstuk 4 neemt een breder perspectief op de zorg voor hemofilie door het zelfmanagement met behulp van een persoonlijke gezondheidsomgeving te evalueren. Waar in hoofdstuk 3 werd geconcludeerd dat mensen met hemofilie meer autonomie wensen, belooft een persoonlijke gezondheidsomgeving om de autonomie en het zelfmanagement van gebruikers te vergroten. In dit hoofdstuk evalueren we kritisch de beloftes en aannames van de persoonlijke gezondheidsomgeving en stellen we dat deze tools erop gericht lijken te zijn twee vormen van zelfmanagement te stimuleren: 'concordant' en 'compliant', hoewel deze vormen niet noodzakelijkerwijs hand in hand gaan. Verder stellen we dat het werken met een persoonlijke gezondheidsomgeving voor sommige mensen ontoegankelijk kan zijn, omdat er veel verschillende vaardigheden voor nodig zijn. Hierdoor bestaat het risico dat reeds bestaande ongelijkheid in gezondheidsuitkomsten wordt vergroot. We sluiten af met aanbevelingen voor designscenario's voor de verdere ontwikkeling van de persoonlijke gezondheidsomgeving.

Hoofdstukken 5 en 6 richten zich op de betekenis van 'genezing', aangezien genezing een van de belangrijkste beloften van gentherapie is en daarmee ook een belangrijke reden waarom mensen met hemofilie gentherapie wensen. In hoofdstuk 5 hebben we de belofte van genezing via gentherapie geëvalueerd door eerst meer inzicht te krijgen in wat er precies wordt bedoeld met het begrip 'genezing'. We hebben een conceptuele rolanalyse uitgevoerd, waarbij we onderzocht hebben hoe genezing wordt gebruikt in vier verschillende medische velden waar het begrip discussie oproept. We laten zien dat genezing op drie manieren gebruikt kan worden: als normalisering van het lichaam, als het verkrijgen van een normaal leven, of als een verandering in identiteit. Aangezien we genezing beschouwen als een praktische

term, aansluitend bij recente pragmatistische bijdragen aan de filosofie van ziekte en gezondheid, kunnen meerdere interpretaties van het concept naast elkaar bestaan, zolang elke interpretatie contextspecifiek is en geschikt voor de functie die het vervult in die context. We sluiten af met het bespreken van drie verschillende situaties waarin de term 'genezing' wordt gebruikt, en onderzoeken de functie(s) die het concept in elke situatie vervult: in de klinische toepassing van gentherapie, in beslissingen over de vergoeding van geneesmiddelen en in beslissingen over de financiering van onderzoek. We concluderen dat het in de klinische context beter zou zijn om de term 'genezing' niet meer te gebruiken, hoewel het in de context van beslissingen over het vergoeden van geneesmiddelen en onderzoeksfinanciering beter is om een meer gespecificeerde definitie te gebruiken om zo te voorkomen dat hype ontstaat of vergroot.

Hoofdstuk 6 begint met een review van het gebruik van het begrip 'genezing' op het gebied van hemofilie. We laten zien dat de meest expliciete interpretaties van genezing te vinden zijn in zogenaamde 'core outcome sets' voor de behandeling van hemofilie, waarin genezing wordt gedefinieerd als een van de belangrijkste behandelresultaten. De verschillende definities van genezing in deze sets komen niet altijd overeen. Zo wordt genezing in de ene set gedefinieerd als een effect dat ten minste vijf jaar aanhoudt, terwijl het in een andere set wordt gedefinieerd als een levenslang effect. Bovendien wordt de term ‘genezing’ regelmatig gebruikt, hoewel deze zelden wordt gedefinieerd. Op basis van hoe genezing in wetenschappelijke artikelen wordt gebruikt, hebben we verschillende kenmerken van genezing geïdentificeerd: het is een eenmalige behandeling, de effecten zijn langdurig, het leidt tot endogene factorexpressie en heeft een positieve invloed op de kwaliteit van leven. Vervolgens relateren we de discussie over genezing aan debatten over de classificatie van (de ernst van) hemofilie en filosofische debatten over de begrippen gezondheid en ziekte. We concluderen dat men in dit veld voorzichtig moet zijn met mogelijke misinterpretaties die kunnen ontstaan bij het gebruik van ‘genezing’ en kritisch moet evalueren wanneer het gebruik van de term wel of niet gepast is.

In het laatste hoofdstuk beantwoord ik de belangrijkste onderzoeksvragen en geef ik enkele aanbevelingen voor de verdere verantwoorde ontwikkeling en toepassing van gentherapie voor hemofilie. Ik concludeer dat er drie overkoepelende ethische thema's zijn. Het eerste betreft de mogelijkheid om aan de verwachtingen te voldoen. Over het algemeen wordt verwacht dat gentherapie een genezing zal bieden en veel van de nadelen van de standaard factortherapie zal omzeilen. Het blijft echter onzeker of deze doelen behaald kunnen worden. Het tweede ethische thema is onafhankelijkheid. Voor veel mensen met hemofilie was de hoop op een onafhankelijker leven met meer vrijheid de belangrijkste motivatie om gentherapie te willen ondergaan. Het is echter de vraag of gentherapie dit doel kan bereiken, aangezien dit ook afhankelijk is van andere factoren, zoals beleid. Ten derde zijn er

vanwege de prijs van gentherapie zorgen over de toegankelijkheid ervan en hoe het middel eerlijk kan worden verdeeld. Met betrekking tot de tweede onderzoeksvraag heeft dit onderzoek aangetoond dat 'genezing' kan verwijzen naar verschillende uitkomsten. Deze uitkomsten kunnen worden bereikt door gentherapie, maar worden niet altijd bereikt door (enkel) gentherapie.

Ik beargumenteer dat verschillende onderwerpen meer aandacht moeten krijgen om gentherapie op een ethisch verantwoorde wijze verder te ontwikkelen en implementeren. Om te beginnen moet de rationale voor de ontwikkeling van gentherapie worden geëvalueerd. Zowel de standaardbehandeling voor hemofilie als de stand van de techniek op het gebied van gentherapie hebben in de loop der jaren vooruitgang geboekt, waardoor verschillende argumenten voor de ontwikkeling van gentherapie zijn veranderd of mogelijk niet meer van toepassing zijn. Ten tweede is het belangrijk om te beseffen dat mensen met hemofilie na gentherapie, zelfs als deze zo effectief is als gehoopt, in een situatie kunnen komen die het midden houdt tussen gezondheid en ziekte, waarin ze zowel 'in remissie' als 'in afwachting' van ziekte zijn. Dit kan de wenselijkheid van gentherapie beïnvloeden. Ten derde kan de vooruitgang in behandelingsmogelijkheden voor hemofilie leiden tot een verandering in de behandelingsdoelen van hemofilie. Daarom is het belangrijk om na te denken over dergelijke potentiële veranderingen en om te evalueren wat vooruitgang, in zowel onderzoek als zorg, kan worden beschouwd. Ten vierde kunnen de verandering in behandelingsdoelen en de onduidelijkheid over de betekenis van genezing de hype rond gentherapie versterken. Ten slotte, alhoewel er momenteel weinig empirische gegevens zijn over een mogelijke identiteitsverandering door gentherapie, kan dit het gevolg zijn van verschillende interpretaties van de betekenis van (verandering in) identiteit. Het is dus een onderwerp dat nog verder onderzoek vereist.

Verder reflecteer ik op de aanpak van dit proefschrift en hoe het onderzoeksproces heeft geprofiteerd van actieve patiëntparticipatie. Ik sluit af met drie concrete aanbevelingen voor de verdere ontwikkeling van gentherapie en hemofiliezorg in het algemeen: reflecteren op de doelstellingen van gentherapie, aandacht besteden aan de ethiek van communicatie over gentherapie, en de zorg voor hemofilie zo inrichten dat de onafhankelijkheid van mensen met hemofilie wordt vergroot.

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About the author

Lieke Baas grew up in Callantsoog, Noord-Holland. After finishing secondary school at the Murmellius Gymnasium in Alkmaar in 2013, she started her BSc Psychobiology at the University of Amsterdam. During this program, she came to realize that she was more interested in societal and ethical aspects of science and medicine than in the workings of action potentials and mirror neurons. Therefore, she continued with the MSc Management, Policy analysis and Entrepreneurship in the Health and Life Sciences and the MA Philosophy, Bioethics and Health, both at the VU University Amsterdam.

After graduating, Lieke worked as a junior lecturer at the Athena Institute at the VU University Amsterdam. In 2021, she started her PhD research at Bioethics and Health Humanities at the University Medical Centre Utrecht. This research, conducted under the supervision of prof. dr. Annelien Bredenoord, prof. dr. Karina Meijer (UMCG) and dr. Rieke van der Graaf, focused on the ethics of gene therapy for hemophilia. During her PhD, she followed several courses in bioethics and philosophy, taught ethics and medical humanities to medical students, and supervised research projects of students. Furthermore, she chaired the Junior Researchers' Board of the Julius Centre for a year. Next to her PhD, she volunteered at the VoorleesExpress Regio Utrecht.

In 2024, Lieke started as a researcher and lecturer in Medical Ethics at the Section Medical Ethics, History and Philosophy of the Erasmus Medical Centre. Among other things, she is involved in the development of the Metamedica education within the new medicine curriculum.

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