

Beliefs and Values about gene therapy and gene editing in patients with hemophilia and their family members

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Abstract

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Hemophilia is an inherited lifelong debilitating disease for which current treatment is non curative. Currently, the promise of gene therapy and gene editing as potential cures are undergoing research. However, we don't know whether or how the hemophilia community will accept them. In this study, we explored the beliefs and values about these new therapies in patients with hemophilia and their family members in order to bring up important research questions as the therapies are being developed.

This is a qualitative study that uses semi structured interviews on patients with hemophilia A or B and their family members. The interview guide is an adaptation of Persaud et al 2018.

Grounded theory was used to analyze the data.

Participants perceived gene therapy and gene editing as a potential curative alternative to hemophilia. Gene therapy, as we described it, is the most accepted however patients and their

family members would like to see more data first. On the other hand, they might not accept gene editing because of safety and ethical concerns.

These data provide directions for supportive interventions to be delivered at the point of choice about gene therapy for hemophiliac patients and family and also make sure the questions that the patients have are answered during the research phase.

INTRODUCTION

Hemophilia is a lifelong debilitating inherited disease.

Hemophilia A and B are rare X-linked recessive disorders which can cause severe bleeding and can require chronic therapy. There are about 1 in 5,000 male births with hemophilia A and 1 in 50,000 births with hemophilia B. Hemophilia A patients have a decrease in their level of factor VIII activity and hemophilia B patients have a decrease in their level of factor IX activity. This inherited disease is characterized by subtype; with severe hemophilia having less than 1% detectable factor while there are also moderate (1-5%) and mild hemophilia (6-40%) subtypes. Approximately, 64% of patients with hemophilia have severe hemophilia. (1) The disease may present at birth with intracranial hemorrhage and without appropriate diagnosis and factor replacement therapy, could be lethal. Later in life, six out of ten young adults with hemophilia will develop comorbidities such as arthritis, liver disease (including Viral Hepatitis C), HIV/AIDS, overweight or obesity. If this genetic disorder is left untreated or it is inappropriately treated, affected patients will have serious health effects for a lifetime.

Factor replacement therapy, an effective therapy, might not meet all the patients' needs.

Existing exogenous factor replacement therapy has proven to be effective, but it is not felt to be a cure. Exogenous factor replacement therapy, which can utilize plasma derived or recombinant factor product, is effective in the prevention and treatment of bleeding. Patients who are on a prophylaxis treatment have approximately 5 bleeding episodes per year. (2)Indeed, one third of those who were treated since childhood are able to discontinue this treatment by age 21.(3)

But while receiving factor replacement therapy, patients still experience a financial and health care access burden. (4) Patients with severe hemophilia generally are initiated on prophylactic factor replacement (prophylaxis) therapy after their first major bleed or as early as when they are able to start walking. However, these options don't represent a cure because factor levels decrease after each intravenous factor infusion, and patients require the medication routinely in order to achieve close to a normal lifestyle. They usually require a require self-infusion of the factor product through a vein at least weekly and usually two to three times a week. Additionally, there is a financial concern that limits the access to current therapy. In 2006, the estimated direct cost per year for a patient that receives prophylactic treatment with recombinant factor VIII was \$300,000 USD which is high enough to be a barrier for patients who need prophylactic treatment. (4) Due to this high healthcare cost, some patients decrease the frequency of which they administer their own infusions or decrease their dosage of clotting factor, (5) even though these changes often result in recurrent spontaneous bleeding. (3) Furthermore, 25% of hemophiliacs between 18 -30 years old are not compliant to therapy because of an inaccessible health insurance or the unaffordable price of factor replacement. In addition, 20% of those patients find it difficult to go to a Hemophilia Treatment Center (HTC), either they feel this critical and comprehensive medical care is a long way to travel, they are unable to take time off or they feel the travel is expensive. (6) Therefore, healthcare insurance costs, medication costs, frequency of factor administration and patient adherence are some of the major limiting factors of consistent use of exogenous factor replacement therapy. Consequently, even though current therapy might be life changing to prevent bleeding episodes and joint damage, there are financial and healthcare access barriers that need to be overcome to meet patients' needs.

Factor replacement therapy does not erase emotional distress, lifestyle and employment challenges in patients with hemophilia.

While some patients have reported an improvement in their factor levels and a decrease in their bleeding rate with factor replacement, family members have reported a constant impact in their emotional distress and quality of life.(7) Even though current factor replacement therapy has improved patient care, patients with hemophilia report a lower physical functioning compared to the general population in the US (1). In addition, children with hemophilia are usually restrained from being fully involved in family or sports activities in order to prevent accidents and hemorrhage, which has a negative impact on their emotional life. (8-10) Moreover, in the US, only 44% of the young adults with hemophilia have a full time job (1) and approximately 1 out of 5 have not been hired for a job because of their condition. (6) So, even though current therapy is effective, due to its costs, its frequent administration and the influence on mental and physical health, it doesn't meet patients' needs yet.

Gene therapy and gene editing are potential promising therapies for hemophilia

Gene therapy and gene editing are promising possible cures for hemophilia A and B that are under study. Current gene therapy methods in hemophilia have used a viral vector to transfer a functional hemophilia gene into the patients' hepatocytes and stimulate a constant endogenous expression of factor VIII or IX. (11, 12) Clinical trials in adults show that severe hemophilia cases are able to be reclassified to mild disease during a 16 month-follow up period. (13) From the safety perspective there is an asymptomatic immune mediated elevation in the liver enzymes, that subsequently has been linked to reduced factor levels.(13) Chronic hepatitis and cancer are potential side effects

which need to be confirmed in long term follow up studies. (11, 12) Despite the purported benefits in the adult population with these gene therapy products, gene therapy has not been tried in the pediatric population yet because the high cell turnover in a child's growing liver may hypothetically result in a vector dilution and a loss of protein expression (14). Alternatively, gene editing uses CRISPR gene editing technology to cut out the abnormal hemophilia gene and insert the correct hemophilia gene sequence in cells.(15) Experiments in animal models show an increase in factor levels. (16, 17) Currently, there is the only phase one clinical trial (NCT02695160) about gene editing in adults with hemophilia B. Theoretically, effects on other sites of the DNA, and miscarriage (if performed prenatally) are potential adverse effects. (18, 19) Even though gene therapy and gene editing will continue to require data from clinical trials to establish their efficacy and safety, they are thought of as a potential cure for hemophilia.

It is unknown if gene therapy and gene editing meet patients' preferences and values.

Gene therapy and gene editing are a potential cure to hemophilia and may represent a solution to the limitations of current exogenous factor replacement therapy. However, before these therapies arrive to the market, it is important to understand what are values and potential barriers that patients foresee before these technologies are implemented. Furthermore, a deeper understanding of the patient's values and beliefs will help plan different strategies to make the medication match the patients' needs because novel therapies cannot succeed without input, acceptance and support from patient communities. So, the values and beliefs about gene therapy and gene editing for in the hemophilia community should be explored before these interventions are implemented.

To our knowledge, there is no study that explores the beliefs and values about the potential use of gene therapy and gene editing for hemophilia in the clinical setting. Previous studies regarding the values of patients with sickle cell disease or Down syndrome about gene therapy have shown that

there are safety, efficacy and quality of life concerns.(20, 21) Factors such as reducing suffering, preventing disease progression might encourage the use of gene modification therapies, while uncertainty of long term effects, trial involvement burden, mistrust due to historical marginalization, reproduction factors, concerns about medication costs and insurance access represent current limitations to the future use of these therapies.(21) Unfortunately due to the unique characteristics of genetic conditions and their communities, we cannot generalize these results to the hemophilia. (6, 20-22) Thus, understanding the opinions of patients and their family members about gene therapy and gene editing is as important as establishing their efficacy and safety. Exploring their beliefs and values is mandatory to understand the patients' motivators and barriers that may later influence the acceptance and adherence of gene editing or gene therapy.

Consequently, we present a qualitative study that explored the beliefs and values about gene therapy and gene editing in patients with hemophilia and their family members.

Methods

Theoretical Perspective

In this qualitative study we utilized an open-ended interview method in patients with hemophilia and family members to explore their perspectives about gene therapy and gene editing. Because, to our knowledge, there is almost no information regarding about the beliefs and values about gene therapy and gene editing in patients with hemophilia and their family members, we used grounded theory, so we could use an inductive process to formulate themes from the collected data. (23)

Participant Selection

We included English-speaking adult patients who self-identified as having hemophilia A or B or adult family members, mostly caregivers. The participants were contacted by an e-mail from the principal investigator through their local chapters associated with the National Hemophilia Foundation. We also allowed participants accrual by word-of-mouth. Once an interested participant contacted the research team, the interviewer explained the purpose of the study, the procedures, the confidentiality and the risks to the privacy of their data. Only participants who agreed to a scripted informed consent were scheduled for a phone-based interview. We interviewed participants until we reached saturation.

Data Collection

Before beginning interviews, two pilot interviews were conducted to assess the quality of the interview guide, and the guide was modified upon the feedback of the interviewees. Then, we performed the interviews until we reached saturation in the group of patients and family members separately, because we expected both groups to have different insights. We did not create separate categories for Hemophilia A and B because they have similar natural history, outcome and management needs. (9, 24)

The interview was based on a previous interview guide that incorporated questions about gene therapy and gene editing opinion studies. (21). The first half of the interview inquired about their experience with the disease. In this section, we asked them about their experience regarding their diagnosis, how this impacted their family, the coping mechanisms used, their current therapy, their current health status, their knowledge about the genetics of the disease and their baseline thoughts about prenatal diagnosis of hemophilia. The second half of the interview aimed to understand their beliefs and values about gene therapy and gene editing. In this section, the interviewer gave two scripted descriptions about gene therapy and gene editing, respectively. About gene editing, we

asked specifically about gene editing in utero and in adults. The third and last section was used to ask about the participant's demographics (age, sex, state of residence, occupation, highest level of education, whether they received education about genetics and where, the existence of other genetic conditions in the family, and where did they get the information about the study). (See Supplementary Table) All interviews were recorded and transcribed using Temi (www.temi.com) and then verified to ensure accuracy in documenting participants' answers. Two people coded the interviews to ensure accuracy of the method. TL assigned a unique identification code to each potential interview subject in the order they contacted her, and transcriptions were only identified by their private identification code, so the recordings and transcripts could remain deidentified and confidential when undergoing review.

Data Analysis

Grounded theory selection entailed a series of analytic steps. First, we had a preset list of codes according to the findings in the previous literature. After listening the first interviews, we refined these codes and added new ones. Then we developed a codebook comprised by unique and well-defined codes. After refining the coding domains, one investigator (TVL) and an external coder applied the codes to each transcript. We used Dedoose qualitative data analysis software (Los Angeles, CA, USA). (25) Once all the interviews were coded, we estimated the Kappa coefficient to measure the inter-rater reliability. Then, we identified the core themes using an axial deductive process.

RESULTS

We interviewed 21 participants (12 patients and 9 family members). Their characteristics are described in Table 1. Our participants' state of residence included Virginia, Texas, Pennsylvania,

Florida, New York, California, Utah, Oklahoma and North Dakota. None of them reported another genetic condition in the family besides hemophilia, except for one mother who had a child with developmental delay of unknown etiology. All our participants heard about the study from the emails they received from their local chapters. The phone interviews lasted between 25 and 45 minutes and were only conducted by author TL.

Initially, we expected to reach saturation in patients' and family member's group separately. However, we found that their reported values and beliefs were very similar. Therefore, we report here on the two groups combined. We note the exceptions in the result section.

1. Unmet needs in current health status

Hemophilia produced a burden on the emotional functioning and quality of life in patients, even in those with a well-controlled severe disease.

Some patients with hemophilia reported living under a huge mental stress because of being exposed to multiple needle sticks to receive therapy for a lifetime. However, most of them followed their prophylactic schedule to prevent any accidental bleeding. Being able to give factor replacement therapy is a tangible item that patients cited to help cope with that anxiety. Patients and family members with a previous familial history of hemophilia coped better with the disease than those who were a new diagnosis in their families.

- *“I think he has just psychological trauma about head bleeds. I think it is unconscious and being killed from that. And, I think that would relieve a huge mental stress. So, he acts like on the outside that everything's cool, (that) he's fine factoring up (and it) is not a big deal.”*
- *“There are so many, you don't have to ... so many people are just not good at managing it. You forget to infuse. And it is one of those things where it's like, I just went in for my treatments, the other for my annual check in the other week and they did an MRI or ultrasound of my ankle. And*

it's like, well actually you have, you know, the fluid from when you got ankle bleeds when you were 12, but it's still there. Well, you know, even it was one of those things. It's like the longer the bleeding can lead to long term damage or arthritis. That's right. So, people will have a hard time with that then I think this (gene therapy) is great”

Most of the patients with severe hemophilia were either on regular or long-acting recombinant replacement factor. The majority of them were doing clinically well with none or few spontaneous bleeds. However, regardless of receiving clinically effective therapy, they were aware that the disease had an impact on their emotional health and their quality of life. They had to limit their activities to prevent bleeding and joint damage. Additionally, there were still people who confessed they were not good at managing hemophilia because they forgot to infuse, or they skipped doses. Thus, the possibility of having a gene therapy available was a mental relief. They were also on multiple medications to deal with the complications of the disease or to manage age -related diseases. Few patients had developed inhibitors, however they saw this as a limitation to current therapy, because it made therapy less efficient.

- *“I mean, it's impacted my quality of life, somewhat personal, like not as much in terms of bleeds. So, I am again, mindful of that being a risk. It's a little bit of a stress to know that my joints might not be as healthy when I'm older because of hemophilia.*
- *“It's controlled fairly well. Um, sometimes I get some breakthrough bleeding just because I don't really go quite by those tricks prophylactic schedule, but generally able to take care of any injuries right away and, and one or two doses takes care of the problems though”.*

- *“I think it's okay. It's kind of a pain to take these, tabs, I often forget and I'm often working. Um, I also just got diagnosed with a fibroid, so that's really complicating the matter as far as the, it's making everything much worse. So, I'm probably gonna move forward with a hysterectomy.”*

Only those patients with the most severe disease or those who had a non-controlled hemophilia despite treatment thought about switching to a new medication.

Per a participant's report, long acting medication had been life-changing, so they thought that it would be a little bit difficult to “jump on the bandwagon” so early.

Even though for most patients it was seen as convenient to get a single infusion of gene therapy or a single episode of gene editing and not have hemophilia anymore, they would rather stay on prophylaxis because the disease was under control. They said they didn't have major problems with their current level of care required, especially for those who were disciplined about infusing. So, it was convenient for them and they didn't want a chance of possibly ruining what was going so great by choosing a new therapy that was riskier.

However, patients with severe disease thought it was more convenient to switch to another therapy to attain a substantial control of bleeds and have their hemophilia status improved from severe to mild. Consequently, they wanted a normal quality of life and infusions only in traumatic events and surgery.

- *“Like, as of now, being fortunate to live in a country where like, I have enough to stay on prophylaxis and not have any major problems with it. I think staying on the current method of prophylaxis, is better than risking gene therapy, although it would be convenient to like get one infusion and not*

have hemophilia anymore. Yeah. But I think it's, I'd rather be safe and like that's my personal opinion."

- *"I think here is different for everybody. Like for me, long lasting has been life changing. But for gene therapy, two primary reasons are a lot of us need to see substantial control of bleeds. Like if you're a severe patient, you can go up to a mild level hemophilia, you can have a normal quality of life and only have to infuse on traumatic events and surgery"*
- *"if we were having this conversation before Friday, my answers may be different because I'm seeing, I am trying to prepare myself for a future, my son is not going to live very many more years. And so, with this new medicine, it sorts of being, I'm hoping it works. But so, if we had this phone call before Friday, my answer may have been yes."*

2. The diagnosis of hemophilia

Awareness about their diagnosis

The participants we interviewed were knowledgeable about their factor levels and the corresponding severity status. However, sometimes their symptoms did not correlate with the reported severity of the disease.

- *"I am, I am. Technically I presented as a severe because I have less than 1% clotting factor, but I really present as like a mild to moderate when, how I bleed, at least as an adult it got better as I grew up a little bit."*
- *"Right. And it's ... When I say moderate, we're on the edge towards severe. It's not, you know what I'm saying is we're just, close to the point where we're severe."*

Usually the diagnosis of hemophilia was challenging

Uncontrolled bleeding was the most common symptom that guided towards the initial diagnosis of hemophilia. However, it was often at first misdiagnosed, for example as child abuse in the case of affected patients and emotional disorder in the case of carriers due to the recurrent joint pain. Misdiagnosis resulted in diagnosis and treatment delay. Age of diagnosis ranged from day 1 to 10 years of age. Receiving the diagnosis of hemophilia was intimidating in patients who did not have much information about the disease.

- “I would fall and bruise up and at some point, someone accused my parents of child abuse and that triggered a lot of alarms. A local (primary care physician) had sort of an idea of what could be”
- “he hit the corner of the table, he got a bump above his left eyelid and it wouldn’t go away for maybe a month. We took him in, and still wouldn’t go away.”
- “I didn’t know. We didn’t know anything about hemophilia, so it was very scary.”

Some participants reported that it was good to know about their genetic mutation, while others thought that it was irrelevant because there was nothing that they could do with that information.

Most people were knowledgeable about hemophilia being an X-linked recessive disorder and how it was inherited. For some of them knowing about the mutation causing the disease was interesting because they could know where it came from, others thought it was not important because it did not change the therapy course of action.

While some women thought that it was useful for family planning purposes, others reported that it was irrelevant because they could not afford to pick and choose some embryos. Some pregnant women whose first-degree relatives were affected by hemophilia thought it was important to know about their carrier status so they could be prepared and have something to look into in case there were any issues during pregnancy or delivery.

- *“I mean, it makes a difference for family planning to understand what your potential is, whether you need to do something like, considering any sperm washing, whereas spurned selection process. When my son was diagnosed, actually my mother called a number of people in the family because there were other expectant mothers. So we felt we needed to let everybody know to be aware so, if they had any issues that that was something to look into.”*
- *“I mean, I can't really do anything with them because I can't afford to pick and choose if I had some embryos”*
- “Interesting to find out where it came from or whatever”

Other carriers and patients who had learned how to manage this condition, did not see the utility of knowing the exact genetic mutation causing hemophilia, because there was nothing that they could do with the result. Furthermore, if gene therapy could be performed, then it would be important to know about their mutation. Also, participants that had a gene inversion causing a severe hemophilia recalled that they perceived that they were not eligible for gene therapy because of their type of mutation.

- *“Have we gotten tested for it? No. I mean it is what it is. So, it's not like I'm going to do anything about it. I just let them know when, I remember after giving birth, they were shocked how much I was bleeding. So, I did tell them there's a history of hemophilia, but, that's it.”*
- *“It's been tested, but I don't know. If I were to have gene therapy done, that would be important. My sister was working for Bloodwork Northwest in Seattle and well, she works there, and so it was kind of accessible. My brother had it first and she had it done. I don't remember (the exact gene mutation).”*
- *“you know, that's a really interesting question because I just found them at my house, and I think we did them in like 1997. Obviously, there have been updates. At that time, they said it was an inversion and therefore my son would be the least likely candidate for gene therapy because even at that time he was diagnosed in 96 they were discussing the possibilities of gene therapy. They told me it would be a decade; it was clearly not a decade”*

3. The potential benefits of prenatal testing in the absence of a curative treatment for hemophilia

Even though there was a lack of awareness about the prenatal testing, it would help to care for the new life

First, very few patients were aware about the existence of prenatal testing for hemophilia. Also, they were not aware what the testing procedure would be. They were not sure if this was a chorionic villus sampling, amniocentesis or a blood test.

- *“Yes, I don't know exactly what they do. I don't know if they do a blood test or what. I know they won't do the needle because of hemophilia and my age, so they wouldn't do that on me. But I think there's a blood test, I think.”*

- *“I mean, how does it work? Ultrasound or, or like a blood test or...”*

On the other hand, our participants expressed that if the information was available, they would use this information to prepare mentally about what to expect, empower the mother, plan about the delivery, get the treatment that the child needs and prepare financially.

Indeed, due to their awareness about the complications of the disease and the lifelong treatment, if gene editing or gene therapy would be available, some participants would prefer to do gene therapy before birth if it was an affordable option. However, others saw it as pointless to perform the test, because there was no current available cure to the disease. Also, because of their increased risk of bleeding, they were concerned about prenatal testing adverse effects such as pain, bleeding or miscarriage. In fact, they wouldn't do the test if it would hurt the baby, especially if there was a risk for miscarriage.

- *“Well, if I know they're doing gene therapy studies, um, yes, it is possible to fix that gene before birth, I think that's fantastic as long as it's safe.”*
- *“I would do it, I think that's wonderful. If there's no chance that it could harm the baby.”*
- *“Being a female bleeder, and doing an amnio or any other tests to get diagnosis prior to birth is already stressful enough to take that risk because when you already are high risk for multiple reasons and then you'd go through the tests to find out your in utero, baby does have hemophilia. At what point are all these tests just going to destroy the baby that I'm trying to have? Because I'm taking this miscarriage risk over and over and over again when I already have this overarching risk”.*

4. Expectations for gene therapy

People expected gene therapy to increase factor levels, prevent hemorrhage, arthritis and joint pain for almost a lifetime

People thought that gene therapy could potentially cure hemophilia because it increased the production of coagulation factor up to normal levels. Consequently, these therapies could permanently prevent future bleeding episodes. Participants had different criteria about what qualified as “effective” gene therapy. They expected to find a success rate between 70-100%. They also expected their factor levels to be above 50%, or an increase that changes the disease status from severe to mild hemophilia. Most of them would prefer preventing spontaneous hemorrhage, while others expected that, if there was any traumatic event, they did not have to worry about factor replacement infusions.

Another expected outcome for gene therapy was no future arthritis or pain. They thought this was achievable by gene therapy because of its potential ability to prevent future joint damage, which in turn would eliminate the pain and the mobility limitations that are long term complications of hemophilia. To call gene therapy successful, its effects should last for at least 10 years said some. Some patients were more demanding and required that the effects lasted for a lifetime in order to call it successful.

- “if it was a one-time shot in a cure and it didn't have any side effects”
- *“You would need it to be 100% and also forever”.*
- ” No joint bleeds, no running to the ER, no, calling the doctor every, you know, I have a call with his hematologist at least once a month because, you know... It's different.”
- *“I just went in for my treatments, the other for my annual check in the other week and they did a MRI or ultrasound of my ankle. And it's like, well actually you have the fluid from when you got ankle bleeds when you were 12, but it's still there. It's like the longer the bleeding can lead to*

long term damage or arthritis. So, people will have a hard time with that then I think this is great”

The use of gene therapy will help people to live a normal life

Participants believed that gene therapy would prevent bleeding and joint damage so successfully that they would have a good quality of life starting from childhood. Furthermore, they could be engaged in sports, traveling and doing other normal activities which they had to be restrained from in order to prevent accidents and bleeding. Consequently, it would relieve a huge mental stress from being always prepared to manage bleeding. Then, as they would not have joint damage, they would not experience other mobility limitations.

- *“If someone could've gone in and fixed that for me health wise it would have been awesome. I say that in a way where I wouldn't necessarily change my diagnosis for other reasons, but I just think of someone like a little boy running around with a helmet on. If someone could've gone in and fixed him before he had to be born and be in pain all the time and have to infuse all the time and I would of course be all for that (gene therapy). That (gene therapy) would be fantastic. Quality of life would be amazing. Much better.”*
- *“I pretty typically get ankle bleeds for example. I'm limping quite lot and I can't really run. So, if gene therapy were a way to make it thought that I didn't get ankle injuries, I think I would be, you know, just a little bit happier overall. Being able to walk normally and being able to more effectively exercise and things like that.”*

Gene therapy might bring better administration schedule compared to current factor replacement therapy

People preferred gene therapy because it would either be one shot in a lifetime, or it would increase the interval time between infusions. Even though participants were aware about the importance of being compliant to their prophylactic treatment because it prevented bleeding and articular damage, it was difficult for them to be compliant to their treatment. Apparently, its frequent infusion schedule and cost of therapy were two of the reasons behind a low compliance. In this way, patients saw gene therapy as promising, because it would eliminate the infusion regimen, and with one shot in a lifetime or fewer injections, they would be able to attain adequate management of their disease and the prevention of its complications. Furthermore, it would be more beneficial for young adults who lived away from their parents or had emancipated from them regarding the management of disease.

- *“Right. I mean, you mentioned that the 20-year mark. I guess, you know, that's what I've also heard that, I guess around the time when, the children go off to college or they leave the house and, the parents are afraid that people will keep up with the prophylaxis, so they've made it through the first 18 years of keeping their joints, hopefully, because the mom or just parents who are in public and to make sure that they are taking their factor religiously. But then we know what happens when they leave the house. The youngsters that kind of be like, hemophilia is not a problem for me. And then they kind of like drop their treatment or they're not as compliant, so I see gene therapy being helpful at that point.”*
- *“I have talked to one young adult who is on it. He hated sticking himself, he was never compliant. And he's so happy, loves, loves, loves. He's just, he's just ecstatic over it. And you know, he joined the trial so he's free and they get followed closely and watched and you know, he didn't really understand what a huge impact and game changer that he was making history.”*

The lack of specialized health care services at every hospital made them in favor of a once every few years gene therapy

Some family members declared that even though there is specialized health care and treatment for hemophilia, not every hospital or treatment center would be prepared to handle emergency situations in patients with hemophilia. In fact, some healthcare providers might not be completely aware of the diagnosis of hemophilia and its treatment. This situation was worse when patients reported traveling to countries where there was no locally available treatment. In these cases, they brought their medications with them to prevent bleeding in case of accidents or other emergency situations.

- *“Having your product available in an emergency if you're unfortunate and go to an emergency room in a hospital that's not a treatment center and doesn't routinely handle hemophilia, that's a real problem, I think. I have visited family out of state and had been in a car accident with both my kids and they were ready to give, one of them of factor eight product instead of the factor nine product. And the ER (emergency room) doctor didn't have a clue. I was the one that stopped it and picked up the phone and cold our hematologist at the time.”*
- *“And just not having to worry about that (infusing). There's never been an issue, but when I do air travel, I take like a backpack full of medicine with me, I just take everything I have”*
- *“My son would no longer have any joint bleeds or muscle bleeds or even the bruising that he has. I would expect that he would be able to fully participate in all the sports that he would want. And that also, I think he has just psychological trauma about like head bleeds. I think it is unconscious and he's being killed from that. And, I think that that would relieve a huge mental stress. So, he acts like on the outside that everything's cool, he's fine factoring up is not a big*

deal. There's always that background of that he's traveling so I'm concerned. What kind of treatment is available in the places that he's going to? he loves to travel. Two years ago, he went to some remote island off the coast of Vietnam and got really, really sick. There was no medical facility on that island. But thankfully it wasn't related to (hemophilia). I believe there's always that you're going somewhere where no one who knows about it, no treatment and no support. So, there's that. Huge quality of life, mental and also just obviously the medical, physical part.”

Patients with severe hemophilia with an underlying diagnosis were willing to participate in a clinical trial

None of our patients had been enrolled on a clinical trial for gene therapy, however, some of them made an unsuccessful attempt to get enrolled in one clinical trial. Per their self – report, they were rejected because their hemophilia was not severe, because they had liver cirrhosis, inhibitors or an inversion in the gene causing hemophilia. In addition, to prevent rejection of the therapy, they knew that immunosuppressive therapy would be necessary.

However, one patient and one family member reported not wanting to start her child on gene therapy because they were afraid of the adverse effects secondary to the long-term administration of corticoids. Even though this was a concern, another participant would still enroll in clinical trials for gene therapy because this would open the gateway for a lot of people to eventually get this new treatment.

- *“Gene therapy sounds to be a good method or a good option for a lot of people. The idea that I have from it is um, going into the trial phases. Obviously, I can't get into it anyway cause I'm just above other testing limits. I'm at 3%, so a lot of the testing is two or below. Yup. Um, the factor*

levels. But if I did have the opportunity, I think I would just, so I could open up the gateway for a lot of people to eventually get something like this.”

- “I can't remember if it was because of his inverted genes or not inverted gene, that that factor right there that he would not qualify at the time and now he was up for any kind of study, you know, being a guinea pig for anything because I need it.”
- “I heard you have to use a not insignificant amount of steroids to kind of quell liver functions and I don't like that either. Well, my daughter has been on steroids for 16 years and she has every single side effect. Associated and they're quite evil. So we just spend a lot of time managing the side effects of the steroids, including adrenal insufficiency. And I heard like something like 12 weeks and three months is not a short time to be on steroids in my opinion.”

5. The potential adverse effects in gene therapy

If gene therapy failed once, they were afraid not to have other therapeutic options for hemophilia

People were afraid that if the new therapy did not work, they would not be able to try gene therapy again or they would not be able to go back to the previous factor replacement therapy. Then, if they went back to their previous treatment but it did not work, they felt then the disease would be worse compared to when they started.

- “It seems like I have read somewhere on the gene on this gene therapy for hemophilia that when it did not work and then the factor did not, the likelihood that recombinant factor did not work.

- *“And, and if, if you were treated once then, would you be able to be re-treated again down the line? You know, or would you burn your bridge? And that's not going to be a option later on down the line.”*
- *“Like you said, if it got in the wrong gene or what the effects would be, if the body won't accept it or if it is accepted, like if you have a transplant, you have to be on those drugs to prevent the rejection.”*

Gene therapy would be accepted only if it has mild adverse effects and it was safer than current factor replacement therapy.

Mild or “*non-consequential*” side effects might be accepted, such as injection site reactions, abdominal discomfort or nausea during the first days, having to do small lifestyle changes like avoiding alcoholic drinks. Indeed, many of them would accept mild adverse effects only if they did not have to infuse again.

However, if gene therapy causes severe side effects such as mobility limitations, deformities, genetic mutations leading to unexpected diseases, cancer and death, then it would not be accepted. Indeed, they believed that any of these conditions could be potentially worse than having hemophilia or would make them go back to their regular factor replacement therapy.

Consequently, they rather wait for 10 to 30-year follow-up period clinical trials to rule out any major side effects related to gene therapy, which they did not expect from factor replacement therapy, because it was safe.

- *“I hope that there aren't. So, I mean, if it is something as simple as, you know, being a reaction to the injection, like at the skin or something like that. I mean that's the, or a little bit of you know, discomfort like nausea or something like that for the first day. That would be the okay. I mean those are non-consequential, but side effects that are more severe that, later on maybe it might develop, I don't know if you would develop some strange reaction of some kind of gene mutation or something that's gonna affect you any other way. Then that would give me pause.”*
- *“I think my roof always stop at if the death is greater than the outcome, my chances of dying for something like this, is more than the actual outcome, then I would, would be opposed to it.”*
- *“This is one of the things in that, call me the really skeptical, like paranoid guy. It's just [sic] we can think that there's nothing wrong, but then, you know, that 10 years later you still learned [sic] there's actually been a side effect that we didn't think about or were not counted for. [sic] And (now) I'm on a treatment where I don't have to really worry about my hemophilia. It's not a big of who I am, but it's not a big part of how it affects my daily life.”*
- *“Will it provoke other medical issues? You know, I've heard a talk about, could it eventually cause cancer? You're thinking of this virus with this product, they have instructions to create factor but could that eventually 10, 15, 20, 30 years from now cause severe cancer where it's just unknow about it. So, you might be having a good quality of life for 30 years but then you know, die because of cancer and least long-term factor hasn't shown it.”*

6. Gene editing is perceived as a potential cure for hemophilia

Only a few people believed that gene editing in utero would bring a cure for hemophilia because it corrected the mutated gene before the baby was developed. In addition, patients would not

have to worry about the current factor therapy limitations, such as playing contact sports, the stigma from frequently infusing, and they would be free from the burden of access to healthcare. Regarding efficacy, participants would basically look into success rate and “bleed numbers” in a very similar way compared to gene therapy.

- *“if the child is going to be born with severe hemophilia, [sic] even though treatments are better today and you don't have to worry about them, [sic] (one risk is) having infection for the most part. In the factors, [sic] they still have their limitations. They still are discouraged from playing contact sports, like football. There's still a stigma while they infuse themselves with a needle [sic] from other friends. You know, some of them manage it better than others, but it's still, it is not fun.”*
- *“Well, what may be some of the positives of the editing? If it did work in kind of a similar way where you corrected the mutated gene before the baby was developed, then maybe it would be helpful for curing some of those types of diseases.”*
- *“I'm free from the burden of access to healthcare. [sic] It would be like my biggest things personally”*

7. The potential adverse effects of gene editing

Gene editing was linked to adverse effects on the fetus, the child and the mother in their participants' mind

There were safety concerns for the mother and the unborn child, because any procedure performed in one of them would affect the other. Several questions had to be answered here.

First, they would like to know if this is a surgical procedure and if it would change the DNA of

the baby. Even though people did not understand yet how gene editing could risk the mother, severe adverse effects would be a red flag.

Also, miscarriage is considered a “catastrophic” event in the fetus. Whether the risk of miscarriage is minuscule or 50%, the participants would avoid gene editing to prevent losing their child. In this way, gene editing wouldn’t be a therapeutic option because there were other effective and safer treatments available. Other unacceptable side effects were deformities or any chronic disease that would limit their health for a lifetime. In these cases, participants would prefer to leave their children “unedited”.

However, just one male young patient said that miscarriage and still birth were better adverse effects compared to the death of the child after birth.

In case they received gene editing, they also were concerned about the need of additional medication to treat unexpected diseases caused by gene editing or if they might have new bleeding episodes that required them to go to the hospital.

- *“it's a procedure that is, and it is so little, and it is inside you, cause you, no mother would like her kid to be worked on while still in there. you just want to have a normal and an easy pregnancy.”*
- *“probably would never happen, but what if there's deformities or [sic] that affected your liver or any bad side effects that you have to live with for the rest of your life. [sic] The transformation in your body that you'd have to live with for possible death. Anything that affects your life long-term, basically.”*
- *“the other one (gene therapy) didn't seem as... Such a big catastrophic end. Even though I know you said that there were some risks or could have some possible risks, (it) didn't seem that (way).”*

No, I don't know what the right word for it is...Catastrophic is about the only way I can think of it that, you know, trying to do this treatment and then, you know, you have a miscarriage or something like that. The other way seems like it wouldn't be that."

- *"So, um, I mean, I think personally I would not do it just because it's, again, not proven to be safe yet. So, yeah, I think I just leave my daughter unedited."*

8. Contrasting gene editing with gene therapy

Gene editing was perceived riskier compared to gene therapy

People thought gene therapy was safer than gene editing. First, gene therapy did not seem ethically wrong because there is no DNA editing which could result in designing your own baby. Second, the risks about using a viral vector seemed safer than gene therapy, which did not have a safety profile established yet. Third, they were against in utero gene editing because it was supposed to be performed on a fetus and there is a potential risk of miscarriage or abortion.

- *"the other one (gene therapy) didn't seem as ... Such a big catastrophic end. Yeah. Even though I know you said that there were some risks or could have some possible risks, (the risks) didn't seem that catastrophic. You know, trying to do this treatment (gene editing) and then, you have a miscarriage or something like that. The other (gene therapy) way seems like it wouldn't be that."*
- *"No like this, this way seems riskier to me. Like the insert that virus envelope one, ...you'd at least have consent of the person doing that, but you know, it's not risking, it seems so much riskier than the other version".*
- *"I mean, it sounds like it would be a good thing for fixing the chronic condition. But I'm just thinking like, if you can design your own kid, down to the height and eye color and height and all*

that and other physical attributes. I mean, that would a little frightening. I'm more comfortable with the gene therapy that's being offered versus the gene editing."

A few people would prefer gene editing rather than gene therapy.

Few people liked gene editing because it could potentially save a lot of the pain and the procedures that hemophilia entails. Also, they understood that there gene editing does not require a viral vector to deliver the medication. One person thought that it was more natural because it used "fetal material" and another thought that "it was less harmful to cause an alteration in a fetus compared to a person already born". Most of the patients and family members thought that clinical trials needed to be done before they decided towards gene editing.

- *"The fact that it could be fixed before, would be fantastic. A Win for all. And, you know, just to save a lot of the pain and procedures with that. But you know, of course the decision would have to be made with regards to the risks."*
- *"It just is better because it doesn't use a virus. I've just learned that they mutate a lot. So, it's very hard for people to put it under control and then just because they reproduce, evolve at a much quicker rate. I feel like it's something goes out of hand. Like it's like really out of hand. We really can't control it. So that's just my concern. If this happens, it could cause harmful symptoms".*
- *"I suppose I would say that I feel like there definitely needs to be more, uh, research and, and trials done". "I actually prefer this treatment over the first one. Because, it's using fetus material. I know that they've done a lot of studies using fetal material for growing organs and stuff and to me, it's the more natural approach"*

Participants weighed factors differently among them when giving an opinion about gene therapy or gene editing

Participants explained that their values were based on their culture, ethnicity, how they had been raised up, religion and the available information about a topic.

- *“You can call it the conservative Asian American values, uh, somewhat similar religious undertone as well, probably what shaped, shaped how I think about the most. Uh, it's just kind of my own moral compass I guess.”*
- *“I guess the implications of the technology. I mean, uh, yeah, to say that it's just restricted to just fixing that particular problem. I mean, it could be, you know, well we're here, we might slowly take something that was kind of pretty much designing your own baby. You know, that kind of, you know, makes me feel a little uncomfortable in that... So, it's kind of like the ethical part of, well, you just don't know where the line is going to be drawn. And as opposed to gene therapy, which is not involving any editing and is done later on in life.”*
- *“Um, I suppose I would say that I feel like there definitely needs to be more research and trials done. And then it kind of raises ethical questions on whether it can be used as, you know, get your kids to have blonde hair and blue eyes or, you know, whatever.”*

9. Common barriers to gene editing and gene therapy

Financial concerns, health care and insurance access were a common concern among patients and family members.

Patients with hemophilia depend on many therapeutic products, which per patients' report, costs around 10 – 15 million per patient. So, patients were stressed about how expensive the therapy was. This was an important concern in the younger population that would be 26 years old soon and would not be covered by their parents' insurance anymore. Also, some of them could not afford to keep up with the biannual medical appointments. Additionally, participants were worried about the costs to the family, because there were families that struggled getting an adequate insurance to cover for the therapy and other related costs.

- *“I think for hemophilia patients in general, especially a lot of us that depend on a lot of product. For the longest time, I was on Medicaid and really didn't see the financial burden of it until I got a job and have to end up paying my own insurance and every single month that I make an order, you know, my hands shake because I'm hoping that my truth provider does actually pay the bill and you know, not deny it, especially with long lasting factor that ends up being more expensive short term although in the long term, if bleeds are completely controlled to avoid, it actually ends up being cheaper. But my hands shake, you know, last year I experienced five months or 12 months that were never paid until the beginning of this year. It's very worrisome. And when you hear numbers, like a million minimum for therapy and up to 10 or 15 million per patient, it's scary numbers. And now that could be incorrect and obviously those are just numbers that are being shouted. But numbers are numbers, dollars or dollars”*
- *“It's also a bit of a stress just knowing how expensive it is. And access to health care insurance, when I turned 26, what am I going to do? I'm not in my parents' insurance anymore.”*

Even though gene therapy was supposed to be cost-effective in the long term, if people could not afford it, it would increase inequity

Participants were aware that gene therapy may be more expensive than factor replacement therapy. But, due to the constraints in factor replacement therapy, gene therapy is more cost-effective in the long-term. Consequently, they would be free of injury and free from the burden to the healthcare industry. However, they perceived a similar situation with long-acting and regular-acting factor replacement therapy. At the HMOs, they evaded the increased costs of the long-lasting factor, so most of the patients were receiving regular acting product. Thus, if gene therapy was very expensive, it would benefit people with higher incomes and people who had an insurance that covered it. Likewise, if gene therapy was completely financially unobtainable, participants would not consider it.

- *“Well, the factor, but I'm referring to right now because, I see that at the HMO, they don't make the long- lasting factor available for a lot of their patients. And I think it's because we kind of shy away from the increased costs of the long- lasting factor. So pretty much most of the patients that are at HMOs, we have a pretty much the same factor, which is the regular acting factor. But I mean, it works for us. I'm not complaining, but you know, if there's something better out there, then they're kind of like shy about using it as it cost more. “*
- *“comparing, you know, the million-dollar shot that maybe you only have, that would save you from years of having to use factor. I mean, nowadays, your average, severe, hemophiliac goes through over \$300,000 worth of factor a year. But if you amortize it over, I guess a little over three years, kind of, made up for that million-dollar shot of gene therapy. So, um, I mean I see it as a saving for insurance companies or medical facilities, but I don't know if they would see it that way. 'Cause it's a million dollar upfront versus, you know, 300,000 a year, you know, for the factor replacement. Because right now I'm currently at an HMO, so it seems like at the HMO they do tend to be very cautious with the cost of things.”*

- “If it were just completely financially unobtainable, I wouldn't take out a loan to get it, I don't think.”

The community expressed their mistrust in the pharmaceutical industry and because of a previous prior blood born viral infectious disease outbreak

Participants from older generations, who remembered that there was a blood born infection outbreak in people with hemophilia were more cautious and would like safer options to choose from. Apparently, this incident was with Bayer pharmaceuticals 15 years ago, when the blood supply was contaminated with HIV and Hepatitis C, causing many patients to get infected. Thus, they did not want to take that risk, no matter if it was a 0.0001% or 30% risk. Additionally, even though they knew that adenovirus was frequently used in gene therapy, in the back of their minds they were asking themselves if it is safe to use it. Participants from younger generations had other preconceived ideas about using viral vectors. For example, the delivery process of gene therapy/ gene editing into the cell made them recall the way HIV stayed in the immune system. Secondly, they were concerned about the virus mutating and causing a new unexpected disease. For this reason, they would not want to participate in clinical trials sponsored by the pharmaceutical industry. In fact, they did not want to be treated like “guinea pigs”. For this reason, they do not trust in any information or clinical trial sponsored by the pharmaceutical industry, because they were assuming that the delivery of gene therapy or gene editing involved a “viral vector” and they supposed that they could get infected again. Therefore, they felt like “guinea pigs”. So, they preferred that the pharmaceutical industry was sure that these new therapies did not increase the risk for any viral infections.

- *“Oh, probably significantly. Um, you know, it was, uh, you know, certainly a situation where, um, you know, he was much more savvy and very knowledgeable about everything that was happening to him. But you know, that generation was, many of them were coinfecting as he was. And so I'm much more cautious about the whole thing and obviously everyone values human life. Just my approach is much more cautious. And you know, I just want my 21-year-old son to be healthy and have options just to have them be options that are safe to choose from.”*
- “I don't want to be the guinea pig. Like I don't want to be the one who in five years BioMarin goes, oops, we actually, you know, we messed up and the virus was actually active or you know, I don't know anything about the science, whatever. So those are all made up reasons but in the same way, 15 years ago Bayer goes, oops, our blood supply was actually contaminated. Sorry, you guys all have HIV. Um, there's no reason for me to even take that 0.0001% risk.”
- “I think safety. And obviously even though the AAV virus, normally is used through a lot of this gene therapy, it's quoted as safe. In the back of our mind is that, we always have this thought of is it safe? Because it's the same thing that happened with blood products, you know, 30 years ago. Yeah. It wasn't safe even though it was tough, so think for me the worry really medically is, is it safe?”
- *I like your study. I like how it's not Pharma based funded.*
- “I think it has to do also with my religious background, I mean, pretty faithful, also, I mean like, it's coming from the generation I grew up in the 80s, and when the factor was contaminated and there was both the HIV and they hep C, which I came down with. Yeah. It seemed like at the time I hear that we had the technology back then to have heat treated the product to inactivate the viruses. But because a lot of the factor would have reduced the activity of the factor in the

concentrate. And so, they didn't opt to go with it, so at that point, they kind of sacrifice safety for I guess profit? So, when something comes to the pharmaceuticals making the right, and the right in the moral or ethical sense that gives me an example of, you know, maybe they didn't make the right choice so that, I'm always a little... I guess... It left a bad taste in my mouth so I'm a little bit more cautious. I guess it's that, definitely.”

There is a concern about the safety on other genes and the health consequences in the long-term

In the case of gene therapy, participants were worried about the possibility of altering another gene and therefore, altering or abolishing its function resulting in unexpected diseases in the long term.

About in utero gene editing, the concern was about changing their DNA. They did not trust in the gene editing technology, especially CRISPR, because editing the DNA (regardless if it edited the right gene or not) could cause a “catastrophic downpour of situations in their bodies”, leading to unexpected medical condition such as blindness and deafness in the long term or in next generations. So, they were afraid about ending up with another disease that could be “10 times worse than living with hemophilia”. Rather, they preferred not having in utero gene editing, considering that hemophilia today is manageable, and people had a normal life with current therapy.

- *“What if it goes into their incorrect place codes for the wrong thing or like cause any other side effects and then the side effects could take like generations to show. So that's my concern about it.”*

- *“You’re already dealing with one difficult diagnosis. And if, let's say you go through it and it doesn't work. And then the child has hemophilia and is autistic and has Down syndrome. And I mean, like they could have all these things. That's really hard. So, you went from this hope to your child living a normal life to 10 fold worse than what it could've been. Yeah. When living life with hemophilia today is manageable and you can happen to me in life and it's not like it was 30 years ago.”*
- *“I think I would also have to add the safety aspect of it. I think, that has a lot of influence just because if it's sort of the scariest thing, the scariest thought about just regular gene therapy when you bring in Crispr, even there, because you don't know if it's going to cause any other issues within your body. Like you might be editing, coding your DNA and it could cause a catastrophic downpour of situations in your body.”*
- *“Yes. With hemophilia or, if there's something else that happens when they do that, something goes wrong and instead he's blind and deaf, you know what I mean? That's a problem too. I'd rather he had hemophilia than be blind and deaf.”*

10. For them, the DNA was considered as the starting point of humanity

People knew that the DNA contained the information that makes them an individual. So, their concern about gene editing was that by editing their DNA, they would “mess around with the DNA”, and it would be like removing something that was part of them and defined them as a human being. Consequently, it could potentially change them so much as a person. So, from the moral perspective, changing who they were as human beings was not regarded as the right thing to do.

- *“Well, just morally for me. It's not right. You don't mess around with DNA.”*

- *“It's just because it changes your... it's just completely changing your DNA. Like it's removing something that supposed to be part of you.”*
- *“your DNA is, where it's, you know, in what makes you an individual, what makes you a human being? I think it's, for me just not right morally.”*
- *“I think it's a scary thought just to choose what you feel is the right treatment for them. Yeah. I think it's even scarier to mess with who they are as an individual, as an actual human being.”*

11. Participants had a concept of identity at the personal and community level

Some participants expressed that if they did not have hemophilia anymore, their identity would change. At the individual level, they did not want to mess with their DNA because once they are what they are, that was it. At the community level, because of their diagnosis, they had built a strong relationship with other people with hemophilia. It was part of their life and they would not necessarily trade that to not being diagnosed with hemophilia.

- *“So, I need to know all that prior to even considering it, but no. I just don't want to mess with people's DNA. It is what it is. Yeah. I mean, once you are who you are, that's it.”*
- *“if I got gene therapy then I wouldn't have hemophilia anymore. Oh, just you know, just like my whole personal identity.*
- *“I've counseled to hemophilia camp for almost 20 years. These people are my second family. I'm very, very, very, very involved. And if this part of my life or to change or go away or if I never had that, my life wouldn't be as good as it is. So, I wouldn't necessarily trade that to not be diagnosed that way”*

12. Gene editing and its potential use for eugenics

Participants expressed their discomfort about gene editing and CRISPR because they could be used for designing their own baby. Participants were aware about gene editing being used for medical purposes and for other “eugenic” purposes. They thought that “it would be awesome” that gene editing brought the cure for hemophilia. However, ethical questions about gene editing and CRISPR arose when they thought about its potential use to change their babies’ characteristics such as the eye and hair color, the weight and cognitive skills. So, even though this might be stopped by laws that regulated its use only for medical purposes, there were people who were not constrained by rules and could use it for eugenic purposes.

- *“Messing with the genes, I know gene therapy, uh, you know, the first type of gene therapy is a virus and that's technically in a way messing, but not messing with your directly with your genes as a sort of messing with your organ when this is taken to an atomic level, if that's correct word to use, but when it's taken to just a molecular level where it's, you know, in what makes you an individual, what makes you a human being?”*
- *“I think gene therapy like very limited in terms of what you can fix with it or change with it. But gene editing sounds like something that you could do for like anything. And then I feel like that might be leading into like eugenics. Cause, like it starts at something for like diseases then it might move on to something more like slippery, I guess. I mean like for other diseases, I guess like being used for medical purposes, fine. But I feel like once you let it, once you permit it for one cause like people will start considering it for other causes. So That's concerning.”*

- *“First of all, I just want to make sure all the countries are on board. Um, the moral conduct, the Moral Code of Conduct and then uh, I would also want at least 10 years of testing.”*
- *“if you can make us a, design your own kid, down to the height and eye color and height and all that and other physical attributes. I mean, that would kind of be, you know, that, that's a little frightening. But, uh, uh, I don't know. I'm more comfortable with the, I guess, the current type of gene therapy that's being offered. Uh, versus I guess the gene editing, I mean, uh, eh, in that sense.*

13. The principle of autonomy and beneficence: parents want to decide on behalf of their unborn babies and children when there is enough information, especially on gene editing

Parents and patients were hesitant about deciding about their unborn babies’ and children’s health while there were still ethical and safety concerns about gene therapy and gene editing. Furthermore, even in the absence of adverse effects, they thought it is scary to choose this therapy for somebody else because it could “mess with their DNA” which defined them about who they were as an actual human being”. Instead, they would wait for the child to be an adult and decide what therapy to use.

In this same way, since the fetus was inside the mother’s body and it would be someone else deciding on its behalf, both the risks for the mother and the baby should be considered in the decision. For example, in the absence of a lethal maternal risk and in order to have a healthy child, the mother could take some risks even though these could lessen her quality of life.

- *“It just sounds like if they haven't been born, it's more of a risk to both the fetus and the mother, and the fact that the fetus can't decide if the risk is worth, [sic] it's someone else (who) is*

deciding, [sic] which is a whole other ethical question. But, for me personally, I feel like if it was deemed safe that would be great, [sic] if it wasn't a huge risk for the mom or the baby.”

- *“Well, as a parent they would have to decide if they're willing to do the risks, otherwise wait the child to get a little older and then make their own, their own decision whether they want it.”*
- *“But if there's a lesser risk of dying and maybe I would have to give up something in life, like I can never run again or, or I could never drink again, you know, like quality of life would lessen. But if, if I can have that and still have a healthy child, I would take that risk”*

Gene editing in adults was more accepted than in utero gene editing

Most of the participants would have preferred to perform gene editing after the baby was born and not in utero to avoid risking the baby and the mother because it had less safety and ethical concerns. In this way they would have more chance to carry the pregnancy full term and avoid adverse effects such as miscarriage. They were also aware that if it was performed in utero might be technically challenging compared to gene editing in adults. Furthermore, they would not want their children (either fetus or children) to be the first ones to try it. They would wait until the results from clinical trials were released and they were 100% sure about its safety before they tried this new therapy in their children. Indeed, applying gene therapy after birth would be a less uncomfortable for them compared to in utero gene editing.

Hence, they were more comfortable about gene editing on adults because the risk to the mother and fetus was riskier than worth it. Rather, they would choose from safer therapeutic options that would come up with time.

- “Well, it'd be different if there was no treatment for it, but I mean, even if the baby was two days old as the therapy would be safer, I would think then doing it when you have a chance for the baby not coming to full term.”
- Well, if it was me, if there's a risk of the baby being aborted, I would wait till they're born and then do it while they were still baby. Yeah. I would think that the risks would be less than. Yeah.
- “(Gene editing later in life) sounds a little less risky in a way, I guess. The technology would be the same. So if they developed the technology to do the gene cutting and insertion in an adult later on in life, the technology would be the same as doing it inside the baby. Just would be more kind of technically, potentially technically challenging.”

14. Religion was a coping mechanism for the management and decision making in hemophilia

People who disclaimed a religious background believed that being “blessed with a life” was a huge fact in itself. Contrarily, using CRISPR technology would be comparable to playing God, because people might use it to “design their own babies”. They believe that God gave them those kids for a reason, because of hemophilia that they had built a strong and close relationship with their kids. Also, because their kids were a blessing to them, they had learned to manage obstacles and issues and they did not want to mess with their kids by giving them a therapy that was not proved to be safe yet. Likewise, they also trusted that doctors could make a positive contribution in the field of hemophilia. Furthermore, even though some of them disclaimed a religious background, their safety concerns were the main reasons to refuse gene editing.

- *“I think it's more cultural. You know, you're given what you're given, and I guess God gave me two kids with hemophilia for a reason. And we are stronger together, it's bonded us closer*

together. So, you know, they're the reason for it. I feel like there's a reason for what you're given. You don't mess with it."

- *"Just the fact messing with DNA prior. I feel like, God has given you the right to be a mom to whatever he has chosen to give you. So, yeah. You know who you go with the flow and you know, there's obstacles and there's issues and you know, you learn to manage."*
- *"I think it has to do also with my religious background, I mean, uh, pretty, uh, faithful, also, I mean like, it's coming from the generation I grew up in the 80s, and when the factor was contaminated and there was both the HIV and they hep C, which I came down with".*
- *"I am Christian. I believe that God put people here to do this work."*
-

15. Participants would like to know if their future generations would inherit the DNA changes from gene editing and gene therapy

Some participants preferred gene therapy because they would not pass the inserted gene or fixed gene to their children. Others would prefer in utero gene editing because it could potentially repair the genetic defect permanently. However, they rather wait the 40 year follow up clinical trials results to observe the effects on their children and grandchildren.

- *"Probably because 40 years after having gene editing, you would have reproduced by then, hopefully. And kind of have hopefully a couple of years maybe seeing how the child would be coming from a family, from a parent that had the gene editing. So maybe, I don't know. I don't even know if I would be able to see in my lifetime then. But a lot of years probably of history with it."*
- *"I would definitely want to know the risk associated obviously with the reproduction"*
- *"Is it going to affect your, your children or your grandchildren?"*

16. Most of the women cared for their babies with hemophilia even in the absence of a curative therapy

In the absence of a cure for hemophilia and regardless their religious background, women expressed that they would continue with the pregnancies and would not abort if their babies were hemophiliacs. Even though they believed in freedom and that everybody should have the option, they thought that aborting the baby they were already carrying was precarious decision. They considered that abortion did not erase the challenges of hemophilia and in the big scheme of things, hemophilia was not that bothersome other than the concerns about the cost and the insurance. In fact, a couple of women felt bad when they were pushed to proceed with an abortion because their babies would have hemophilia. Indeed, one of them had a bad experience because her insurance would not cover a prenatal procedure (likely CVS) if she did not agree to abort the baby if it had hemophilia. Even though she felt desolated about being pushed to perform an abortion, she still got tested and continued with the pregnancy of her affected child. Likewise, under the same concept of freedom, one woman who wanted to have children, decided not to have any more children because she could not afford to pay assisted reproductive technology.

Contrarily, a couple of men contemplated abortion as an option, but they were not strong about it.

- *“The risk of doing an Amniocentesis, um, with twins, you know, for miscarriage risk is very high and then it was prohibitive to do any other kind of testing. And I realized that, the testing wouldn't tell me anything that was any different course of action. I was asked, why I didn't abort? so that I wouldn't do, and I didn't do selective implantation. So, I was asked why I was going through with this pregnancy. I didn't know their status and that's stuck with me. I wouldn't have aborted if I had known they were hemophiliacs.”*

- *“one shouldn't, uh, abort the fetus if it's positive because in the big scheme of things, I don't think hemophilia is that bothersome other than the concerns about the cost and the insurance and stuff like that.”*
- *“It would definitely give families of notice what to expect. I suppose there's a potential for families to say, well, maybe let's just take care of this (abort the baby) before it comes out. But I don't really have an opinion on that one way or the other.”*

Carrier women need to be supported by the health care system and medical providers

Local primary care providers and emergency doctors did not think about hemophilia as a cause for recurrent and unexplainable joint pain in young females. Instead, these women reported receiving care for a mental disorder before they were diagnosed with hemophilia. Furthermore, there was no support for carrier women with no children who were planning motherhood or who might benefit from gene therapy or gene editing.

- *“I'm ice skating I'm doing gymnastics, here my ankle, my knees, my hips, my wrists, my elbows, and my shoulders were constantly swollen and in pain. Um, our local ER, I think at that point had told my parents that we can't explain why she's swelling, but we think she needs to speak with, um, a specialist because we think she has some mental things going on”*
- *“I mean I would be open to any other resources. Um, I think for me being a carrier, I don't believe there's a lot of support. There are women who were carriers who now have children. Um, so there's that. But I don't believe like at my stage in my age, there's a lot of support for people who without children and to kind of prepare our future motherhood or something like this.”*

17. What would patients and family members want to know about gene therapy and gene editing?

Updates about current and further therapeutic options given by medical providers and HTCs with no conflict of interest

Their main sources of information were the HTC, healthcare providers, key opinion leaders in the hemophilia community from social media and medical journal articles. Participants who were in a scientific field preferred reading peer-reviewed and published articles. Participants who were more active in their community had more access to information from the pharmaceutical industry. However, giving patients information from an unbiased source will help them have a complete knowledge about the available options and give informed consents based on a true autonomy

- “And then also magazines like HemAware. I read the articles there and I also get some email blasts and go over articles that are pertinent to hemophilia. And a lot of times they also go over new treatments that are in clinical trials also and, you know, kind of updates on how they're doing.”
- “Oh, it'd be great for it to be channeled through Kelly Communications. K. E. L. L. Y. Remarkable woman. She's a psychiatrist. He had a son with a bleeding disorder. She's published. Tons of information on her.”
- “As long as it's from a neutral source, but like not like the pharmaceutical companies or like, the are researchers that are developing, uh, the procedure itself. They're probably going to be biased for it, but as long as they're a fair source, like credible source, like the doctor or the hemophilia society, I think I would be fine.”

- “ I think that really people need to understand what they're doing. Like, this kid I talked to with gene therapy has no idea. What made you, because I was really curious like, what made you join this trial? I can't believe it. He was like well, I just didn't want to, you know, infuse myself anymore. I'm like, oh, there's hemlibra, yeah. I couldn't even.... . I didn't say that. Of course. No, but yeah,”

Participants would like to hear successful stories

Before they considered gene therapy, they also wanted to hear successful stories about patients who underwent through this therapy and no longer needed clotting factor, had no major adverse effects and could live a normal life without the obstacles that individuals with hemophilia usually do.

Testimonies from patients who received in utero gene editing would not be helpful because they would be disease free from birth and would not have experienced the emotional and physical burdens and quality of life limitations of a life with hemophilia. In these cases, patients and their family members they rather look into the efficacy and safety in clinical trial results first.

- *“ But for me to feel more comfortable with it myself, I would want to do some research on others that have already experienced the procedure. At successfully and that they're doing great. Yeah. And you know that now they no longer need their clotting factor. Um, you know, I'd like to see some that were successful with this. As much as one or two years prior and they're still doing great.”*
- *“I mean I can try, I mean, one success, like does this person no longer have hemophilia and no longer has to take infusions and like can they live a more normal active life without the obstacles that individuals usually do with hemophilia?”*

More clinical trial results, so adult population would make informed decisions about switching to gene therapy

For our interviewees, factor replacement therapy was successful at preventing hemorrhage and articular damage, with no major safety concerns. Thus, they did not want to change their current medication for a new therapy that has not been completely studied yet. They would want to see clinical trial results with longer follow up periods (10 – 40 years), a large number of participants (more than 50), and a safety profile.

- “I mean, I think it's just all new. It's an incredible blessing in other communities where disease groups like SCIDs severe immune deficiency. Incredible. Life-changing, you're blind -- now, you can see, yeah, sign me up tomorrow. But with hemophilia, there is treatment now and the treatment allows people to live normal, normal life expectancy. So it's a little bit difficult to jump on the bandwagon so early.”
- “They expect that most of the participants believe that more studies are needed in order to know the outcomes of gene therapy before deciding for it. However, in gene editing, people recognize it as a potential cure, but would refrain from using it because of safety or moral concerns. “
- *“Potentially it could be affecting like the babies’ babies and other things, so, yeah. It's just to hard to tell when you're talking four generations down.”*

Clinical trials in pediatric population are needed

Participants expressed their need to see the results of clinical trials for gene therapy in children. If these studies showed that children were able to live a “normal life” and that there were no side effects, before they tried it with their own children.

- *“I guess once I see more studies on kids for gene therapy, I wouldn't mind considering it, honestly. Yeah. But I haven't seen any studies on children. You know, and I can see why. I mean probably to their liver still expanding and growing. But you know, once it's studied, and if it works, by all means, you know, I give them the option, you know, what do you want? there's this new thing out there now. do you want to try, not try? Yeah. And then we take it to the doctor.”*
- *“I mean, if they're able to live a normal life, like any other child then go for it, by all means. I wouldn't hesitate in putting them on, but you know, I will need to make sure that that is a probably, you know, there is no side effects to it.”*
- *“I mean, it's great, but I just don't feel like it would work for my kids because their liver is still growing”*

They would like to know the logistics of gene therapy

The participants would like to know about how gene therapy and gene editing administration schedule and treatment requirements. For example, they would like to know whether they needed to make any lifestyle changes, like not drinking any alcohol. They would also like to know about the frequency of the follow up visits and the manufacturing procedure, especially for gene editing. In addition, they would like this information to be delivered by a neutral source, not by a pharmaceutical company.

Gene therapy

- *“I guess I would ask them, you know, how long they had to wait for it. Was there a waiting list? Can you have the procedure done anywhere or is there like just one state or one? I mean, I know it's really rare. Would be rare to begin with and you know, then what the follow-ups are?”*
- *“Like if it's just like you said, if it's, you know, you, you'd have to know like if it's a sequence of treatments, you gotta do this every week for a year. Is it one time and done? Is it, you know, whatever that would be.”*

Gene editing

1. *“I mean this one just sounds a little different to me too and it's probably like, maybe I'm just like in my head think of it as if like where did they get this? Like, do you get like a donor gene? Like where did they pull that?”*
2. *“Okay. Uh, I would want to know more about how they actually work. Like the statistics about which genes they're moving, like how the virus finds its way to the liver. Then just more information on the science side of it, just so that I could, since your safety and maybe judge for myself how efficient is going to be. Is it worth that risk and stuff like that.”*
3. *“As long as it's from a neutral source, but like not like the pharmaceutical companies or there are researchers that are developing the procedure itself. They're probably going to be biased for it, but as long as they're a fair source, like credible source, like the doctor or the hemophilia society, I think I would be fine.”*

Insurance related concerns regarding gene therapy

It seemed that most knew gene therapy would not be covered by insurance because it remains an experimental therapy. However, if gene therapy became approved therapeutic alternatives for hemophilia, they were concerned about:

-Could they recover their therapy if they change insurance?

-Who is going to pay for the later complications of gene therapy whether it was accessed through a clinical trial or commercially somewhere?

-Will insurance companies even pay for this therapy, even though because they may not gain the benefits because people will change insurance companies later on?"

- *“That is there are complications to gene therapy, whether they get the gene therapy on a clinical trial or commercially somewhere, who's going to pay for those complications.”*
- *“And also I'm concerned because being involved for so many years, we see so many companies bought out and changing names is how is the patient covered, not just through the study but after the study if any complications arise and who pays for this kind of things.”*
- *“Because insurance companies don't want to pay for something if they consider it experimental. So I think with both of these, they would certainly be considered experimental. They would not be looking at the bottom line that well, if we paid this much one time, yeah, we're going to save all this money for the fact that they would use the rest of their lives.”*

DISCUSSION

In this study, we found that participants perceived gene therapy and gene editing as potential curative alternatives for hemophilia. However, they recognized the differences between both, and they preferred gene therapy as we described it.

Regarding gene therapy, they valued a sustained efficacy and they expected more studies that established its safety in the long-term. Similarly to the patients' values found at the 1st WGH Gene Therapy Round table, our patients expected an increase in their factor levels (26). Additionally, our participants hoped that gene therapy would decrease the bleeding episodes and increase its durability. Contrarily to the participants' expectations about the lifetime effect of gene therapy, clinical trials thus far shows a 2- year effect durability for gene therapy which improve their severe status to mild (13, 14). After 6 year follow-up study, which is the longest -term data published to date, reports that 50% (3/6) of the patients with Hemophilia B discontinued prophylaxis, while the other 50% improved their status to mild hemophilia, with no spontaneous bleeds, so they increased the length of time between treatments with factor to cover for the bleeding episodes after trauma or surgery. (11) According to our results, our participants also expected to have their hemophilia status improved to mild hemophilia. Additionally, the expected outcomes outlined by our participants, such as an improvement in the factor levels, a decrease in the bleeding episodes, joint damage and pain, normal quality of life, and the improvement in their emotional health, are also considered in the CoreHEM Multistakeholder Project , which was created to standardize the gene therapy outcomes among clinical trials, providers, and patients. (27) Even though our participants supposed that gene therapy has no major adverse events such as cancer or death, they preferred long term results from clinical trials before they accepted this therapy. The major adverse effects that they were concerned about is death, unexpected disease from vector and gene integration,

cancer, liver disease and adverse effects from immunosuppressive therapy. In a similar way to what patients have heard about the rejection to gene therapy, short -term follow-up phase 1-2 studies have shown an immune mediated transaminitis which resolves after a short trial of corticoids. (28) Similarly, adenovirus vectors have shown to produce low tumorigenicity,(29) it is important to contrast experimental study results to long term follow up clinical trials. Thus, we also recommend establishing a registry that provides real world evidence that could help clear the long-term safety concerns in gene therapy. (26)

Many participants were worried that gene therapy wouldn't work if it was given for a second time after it lost its effect. Some participants mentioned that it might happen due to a rejection to gene therapy, however almost none of them precised an exact mechanism for it, such as a vector neutralizing response from the host. Having the awareness of this mechanism will facilitate the understanding that their organism will recognize the virus and prevent a possible infection. Another long-term adverse effect that they did not think about was thrombosis. (27)

In our study, the main barriers against using gene therapy were 1) having a controlled disease with current factor replacement prophylaxis and 2) cost, insurance and health care access concerns; while for in utero gene editing, the main barriers were ethical and safety concerns. In this case, the ethical concern were about 1) the potential eugenics purpose of gene editing and CRISPR technologies and 2) the correct use of the autonomy and beneficence principles, when parents had to decide on behalf of their fetus.

To our knowledge, this is the first qualitative study that reports that patients with a controlled disease prefer to stay in their current therapy rather than switching to gene therapy or gene editing. As found in other studies, most of our participants had severe hemophilia and are under prophylaxis. Similary, to what is reported elsewhere, our patients who started treatment early in

childhood have been able to prevent bleeding episodes, however, they have not been able to discontinue prophylaxis yet. (3) So, it is understandable when there are existing therapies that can result in a normal life, patients are more reticent to try new therapies with less established efficacy and safety. Contrarily, for example in the case of sickle cell disease, when their therapeutic alternatives are less promising because of the shortcomings of current treatment options, patients are most likely to accept gene editing. (21)

Similarly to our study, patients and family members who experienced regular acting factor replacement therapy were the ones who expected more effective and safer longer acting therapies with less frequent injections, with an improved manageability, which lead to a better quality of life in terms of independence and flexibility. (30) In addition, besides the emotional burden that living with hemophilia brings, patients and family members, especially those who are not familiar with the treatment of the disease, experienced emotional and practical challenges regarding their children's treatment due to repetitive venipuncture. Likewise, another factor that creates anxiety is not encountering health care professionals who are familiar to hemophilia and its treatment, especially in emergency situations. (7) Consequently, in our study, patients and family members expressed that gene therapy, which has shown to be efficient and safe in the short term, is a potential solution to the problems of prophylaxis administration. However, some of our participants were inclined to idealize gene therapy, thinking that it could potentially be one-time injection. So, even though it is yet unclear how the administration schedule of gene therapy will be, patients and their family members need to be educated about this new therapy.

The participants in our study were aware of the cost-effectiveness in gene therapy, because in the long-term it might theoretically have a more convenient administration schedule and potential improvement in quality of life compared to current factor replacement therapy. However, for them,

the cost would be a limiting factor in their decision-making process about receiving gene therapy. For this reason, another core outcome for success in gene therapy is the utilization of healthcare system.(27) Even though, it is foreseen that it will have a high price initially, it is expected that insurance companies and decision makers set up a price considering the averted costs due to hospitalizations, emergency room visits because of bleeds, inhibitors, infusions, pain, other medications, homecare services, consults and professional family members. (27) Indeed, Nathwani estimated a financial savings over £5M, in 6 patients that received gene therapy over a 6 year period. (11)

Even though we didn't asked about their willingness to participate in clinical trials because it was not the aim of this study, few of them who were not successful enrolled (because they had viral hepatitis, they have had inhibitors, or they had mild hemophilia) spontaneously expressed their interest in participating in a gene therapy clinical trials in the future. Despite that we did not probe for the reasons behind their willingness to participate in clinical trials, one of them expressed that "he would do it to open the gate way for gene therapy to others", which is compatible to the concept of altruism found in another study. (21) However, to have a better picture about it, we recommend to further explore their motivations and barriers, qualitatively and quantitatively, towards their participation in gene therapy clinical trials for hemophilia. Pending reasons to be explored are compliance concerns, safety concerns, mental health issues, etc.

Our participants expressed their need to see the results of clinical trials for gene therapy in pediatric population with hemophilia, before they consider gene therapy for their children, in the same way with the results described in Pierce et al (26).

We can say from our data that the barriers for treatment adherence were the complexity in the management of the disease and the inability to afford the costs of it. In fact, it was clear that parents

and young patients main concern was how would they have access to the medication and if they were going to be able to follow the schedule. Indeed, Lee Mortensen et al described that adherence to prophylactic treatment in young adults is attained when individual patient needs and preferences are considered when planning treatment. (31) So, the fact that sometimes regular or long acting treatment prevents patients from having a normal life is an opportunity for gene therapy.

To our knowledge, this study is the first study to explore gene editing is perceived as a potential cure, in utero and post-natal procedures were perceived to have safety and ethical concerns. Only some of them would proceed to post-natal gene editing. However, patients with severe inherited untreatable conditions would accept gene editing (32)

A miscarriage, an abortion and adverse effects in the mothers were the main reasons why participants won't do in utero gene editing. Unexpected health consequences resulting from the genetic modification were also important deterrents. In fact, if pursuing it in the post-natal period, they preferred a well established efficacy and safety because they wouldn't like their children to be 'guinea pigs'. Additionally, to know about its effects in future generations, they would like to know what the results 40 years after gene editing was administered. Persaud et al described that parents, patients and physicians were concerned about long term effects of gene editing. Similarly, one study about the beliefs towards somatic gene editing within the sickle cell community, also found that one of the reasons why parent's or patients wouldn't perform gene editing was because "they don't want to mess with their/ their child's" genes or "I don't want to change one condition for another" (21) Likewise, the American College of Medical Genetics states that gene editing in embryos has safety and ethical concerns because of the unpredictable health consequences in the embryo and in future generations which could be recognized in the long term. (33) furthermore,

the National Institutes of Health recommended that prenatal gene transfer for research, should always be done with the maternal and sometimes paternal consent, from a personal commitment rather than as a response to society's interests' purposes. (18) According to this statement, there are other risks to the fetus besides spontaneous abortion, such as blood sampling related anemia resulting in congestive heart failure, destruction of transduced cells or the destruction of residual native function. For this reason, it recommends a prenatal gene modification therapy for untreatable disorders that have accurate diagnostic methods early in the pregnancy.

From the ethical perspective, this statement encourages a benefit risk assessment before performing prenatal gene transfer. In other words, it supports prenatal gene transfer if the harms to the preborn baby and the mother are minimized, the potential benefits for the fetus are maximized and the germline effects are minimized.(18) Consistent with the best interest standard principle, in which usually parents and family members place their child's interests above their own, (34) we found out that almost all the patients and parents wouldn't like to make a decision on behalf of another individual (the embryo) if the intervention was lethal or could have other undesirable and unexpected health consequences.

Similarly, to other studies, our study showed that there was a strong sense of identity and belonging in the community. Even though most of our participants were somehow linked to the Hemophilia foundation, in general, they expressed a sense of belonging because the foundation has been advocating for them which has resulted in a variety of treatment options and convenient health care services at their HTC's. In fact, if they were cured from hemophilia, they will find it "weird" to live without it, and they will lose their identity in their personal lives, within their families and community. (26) Furthermore, this concept of identity started in the concept they have of DNA, as the "molecule that defines them as who they are". Therefore, any modification made into their

DNA would change them as a person. (21) Consequently, based on the principle of autonomy, they believed that they cannot decide to make such an integral change on their child's life if they decided to pursue gene editing.

As previously reported, people perceived prenatal screening useful to make informed decisions and be prepared for the management of the pregnancy, delivery and after birth. However, the main disadvantage for them was a lack of utility in the absence of a therapy that could change the course of action with no curative benefit in childhood. (35) Additionally in other studies, prenatal screening increased the awareness for the disease and 90% of the participants disagreed about pregnancy terminations because of a diagnosis of hemophilia. (36) Similarly, a study in genetically disabled adults revealed that 65% of them were against selective reproduction. Furthermore 85% of the patients with Hemophilia were against selective reproduction because they perceived their genetic characteristic as part of their personal identity. And similarly to what our female patients who were planning on motherhood and male patients expressed, strategies should be performed to remove social and environmental barriers. (37)

Additionally, our participants based their decisions on their ethics, safety and efficacy of gene editing and gene therapy, costs, insurance and health access, their previous experience with hemophilia and religion). Some participants reported that their values were not based on morality. However, we could not probe if by morality they were referring to its actual meaning (the ability to distinguish if something is proper and improper) or something different.

As reported by Persaud et al (21), patients and their family members would want to be educated about the gene therapy and gene editing manufacturing process, the administration process as well as updated information about its research studies, including the clinical trials.

This is also the first study to report that patients would like to hear from people with hemophilia who had a successful gene therapy as evidenced by an increased in the factor level concentration, a decreased bleeding rate, no or minor adverse effects, a normal quality of life and emotional life.

Our main limitation is selection bias. Our participants were contacted through the hemophilia foundation. Thus, we might be identifying the opinions of the people who are more engaged to the community. However, our results are similar to the findings from patients about how they feel about the disease are the same as other qualitative or quantitative studies. We also did not ask about religious affiliation or how spiritual they were. Rather we let them spontaneously disclaim if their religious beliefs influenced their beliefs and values about these therapies. In further studies, we suggest using a Likert scale to measure how religious they are. Neither we asked them about their political affinity. We might have a selection bias, because we noticed that political views might have been an influence on our results. Even though we tried to sample a similar number of conservative and liberal states, we got less response from the conservative states. For further opportunities we recommend to ask each participant about this characteristic if we think that it will influence the results. However, in this study, the beliefs about controversial topics such as abortion was similar regardless their religion or political views.

Our biggest strength is that this is the first study to report beliefs and values about gene therapy and gene editing as therapeutic options for hemophilia in patients and their family members. In fact, that this study was not driven by a pharmaceutical company, and the patients were not contacted through medical professionals. In this way, we don't have an interviewer, information bias or social desirability bias.

CONCLUSION

Our main conclusion is that patients and family members preferred to use gene therapy, even though they would like to see more results about its safety and efficacy first. Gene editing was not perceived as a therapeutic option because of its ethical and safety concerns. Also, patients would like to 1) hear about successful stories or other patients who have tried gene therapy, 2) whether they can try again gene therapy or factor replacement therapy if they reject gene therapy, 3) the logistics and manufacturing process of gene therapy and gene editing, 4) results from studies in pediatric population before they try gene therapy on their own children, 5) more long term follow-up studies from clinical trials in adult population to know about the adverse effects, 6) insurance and cost barriers when accessing gene therapy and gene editing.

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Table 1. Characteristics of the people who participated in the interviews

Characteristics	Patients n = 12	Caregivers n = 9
Age	36 (18 - 75)	51 (40 - 67)
Sex		
Male n(%)	9 (75)	-
Female n(%)	3(25)	9 (100)

Severity of Hemophilia in patients or children		
Mild n(%)	1 (8)	-
Moderate n(%)	1 (8)	-
Severe n(%)	10 (84)	9 (100)
Race		
Caucasian n(%)	6 (50)	7 (78)
Asian n(%)	1 (8)	2 (22)
Black n(%)	0 (0)	0
Ethnicity		
Hispanic n(%)	3 (25)	2 (22)
Non-Hispanic n(%)	9 (75)	7 (78)
Highest Level of Education		
High School n(%)	1 (8)	0
College n(%)	3 (25)	4 (45)
Bachelors n(%)	6 (50)	2 (22)
Graduate Student n(%)	2 (17)	3 (33)
Teaching about genetics		
School n(%)	1 (8)	2 (22)
High School n(%)	6 (50)	5 (56)
College n(%)	3 (25)	1 (11)
Don't know/ Don't remember n(%)	2 (17)	1 (11)

Supplementary Table

AIM	QUESTIONS
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<p>1) To know about the preconceptions about the disease.</p>	<p>1) How did hemophilia affect your family? 2) How many members of your family have hemophilia? 3) What type was it? 4) In case your child has hemophilia, what age was it diagnosed? 5) Was the diagnosis made prior to your birth or at the time of birth? 6) How did you feel like his first year of life prior to starting therapy for hemophilia? 7) How did you cope in that first year of life with the diagnosis? 8) What is your opinion about your knowledge of the available treatment options for hemophilia A? 9) Where do you get your information about treatment options from? 10) What type of therapy have you personally/family member been exposed to before? 11) What other therapy were you told about as an option for you? 12) What is the current therapeutic approach that the patient is receiving? 13) What is his current health status? 14) Can you explain the genetics of hemophilia? 15) Why do you think it may be important to know your genetic results for hemophilia? 16) Are you aware of prenatal screening or testing for hemophilia? 17) If so, what is your opinion on this type of screening? 18) Would you change your mind about prenatal screening if gene therapy or editing became available?</p>
<p>2) To Explore the patients' and caregivers' opinions about gene therapy</p>	<p>1) What do you think of gene therapy? 2) What might be the pros of such therapy? 3) What about it bothers you or causes you concerns? 4) How would this change your ideas about prenatal diagnosis and genetic diagnosis?</p>
<p>3) To Explore the patients' and caregivers' opinions ideas about gene editing.</p>	<p>1) What do you think of gene editing? 2) What might be the pros of such editing? 3) What do you think of editing could be done prior to birth? 4) And what about it bothers you or causes you concerns? 5) What level of information about this therapy would you want to know before you thought about this for your own family?</p>
<p>4) To know about the participants' demographics</p>	<p>Age (of the participant and the first- degree family member with the disease), gender identity, race, ethnicity, occupation, highest level of education, whether he or she were taught about genetics in school, what level of education was this at, history of other genetic disease in the family.</p>

