

The Hemophilia Gene Therapy Patient Journey: Questions and Answers for Shared Decision-Making

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Purpose: The anticipated emergence of hemophilia gene therapy will present people with hemophilia (PWH) and treating clinicians with increasingly complex treatment options. It will be critical that PWH and their families be empowered to participate fully in decision-making through transparent communication and the development of targeted educational resources.

Methods: The Council of Hemophilia Community (CHC) convened across a series of roundtable meetings to define the patient journey for hemophilia gene therapy, and to develop a question-and-answer style resource to guide discussion between healthcare professionals (HCPs) and their patients. Patient groups were also consulted during the development of this tool.

Results: The CHC defined 5 key stages in the hemophilia gene therapy patient journey: pre-gene therapy (information-seeking and decision-making), treatment initiation, short- and long-term post-gene therapy follow-up. PWH will have different questions and concerns at each stage of their journey, which should be discussed with their HCP to aid decision-making. The resulting patient journey infographic and Q&A resource (see [Supplementary Materials](#)) has been developed for HCPs and PWH to provide a novel and practical roadmap of key issues and considerations throughout all stages.

Conclusion: These resources support a collaborative, patient-centric, shared decision-making approach to inform treatment decision discussions between HCPs and PWH. The value of such discussions will be influenced by the language adopted; health literacy is a particularly important consideration, and these discussions should be accessible and tailored to PWH. HCPs and PWH can benefit from awareness of the common questions and uncertainties as they progress together along the patient journey. While the contents of this article are specific to hemophilia gene therapy, the concepts developed here could be adapted to aid patients in other disease states.

Keywords: hemophilia, patients, HCP guidance, health literacy, disease awareness, treatment landscape

Introduction

Limited literature is available that combines the concepts of the patient journey in hemophilia gene therapy with corresponding life stages. As clinical developments to address the unmet need in hemophilia advance there is also a great need to address the educational and clinical decision-making challenges that will follow market authorization. Herein, we provide a new, interactive, question and answer (Q&A) PDF resource (see [Supplementary Materials](#)) for shared decision-making along the patient journey.

The Unmet Need in Hemophilia

Hemophilia is a rare X-linked recessive genetic disease, with an estimated prevalence of 17.1 and 3.8 cases per 100,000 males worldwide for hemophilia A and B, respectively.¹ The current standard of care for severe hemophilia, in countries where it is available, is prophylaxis with factor or non-factor replacement therapy, which aims to prevent bleeds and greatly improves patient outcomes and quality of life.² However, people with hemophilia (PWH) remain at increased risk of bleeds (including

joint and post-surgical) as well as hematomas (and ensuing synovitis and joint disease)³ and life-threatening intracerebral hemorrhage.^{4,5}

As single-gene disorders, hemophilia A and B are promising candidates for gene therapy. Introduction of the missing *F8* (hemophilia A) or *F9* (hemophilia B) gene aims to deliver a potentially long-term, functionally curative treatment by restoring coagulation factor production to clinically effective levels. Simultaneous goals include ensuring no vector- or transgene-related toxicity and broad patient eligibility across age groups and in patients with inhibitors.^{6–8} Gene therapy can therefore offer a new therapeutic option within this treatment landscape, to fit the needs of each individual.

Different gene therapy products are likely to meet varied unmet needs of PWH. While several hemophilia gene therapy clinical trials are in progress, no product had been approved at the time of publication.⁸ Among the approaches in development, adeno-associated viral (AAV) gene transfer solutions are the most advanced in clinical trials, though these products have different constructs, serotypes, promoter/enhancer regions, and manufacturing methods that will affect patient eligibility and choice.^{8,9}

Defining the Patient Journey

The gene therapy patient journey extends throughout all life stages for PWH—from birth/diagnosis through to later adulthood—with different checkpoints corresponding to patient life stages. The constantly evolving treatment landscape involves numerous decisions that require guidance and support from healthcare professionals (HCPs). The patient journey for PWH undergoing gene therapy in particular can raise common concerns and experiences, eg, understanding benefits, risks, adverse events, impact on quality of life, and eligibility.¹⁰ Therefore, full transparency and personalized information about the existing knowledge, therapeutic options, and unmet needs are essential to empower PWH to make informed decisions before, during, and after treatment.^{7,10–12}

Patient Centricity and Shared Decision-Making in Clinical Practice

Current Gaps and Limitations

Patient engagement and personalized care are gaining attention in medication development, validation, and adoption, beyond the more traditional emphases on safety, efficacy, regulatory aspects, and communication with HCPs. PWH are typically instructed about their current and future treatments, rather than engaged in conversations and decision-making on treatment options.¹³ Often, healthcare materials are written at a technical level in what may be the patient's second language.¹⁴ This has made it difficult for them to access, interpret, and apply health information to their decisions, contributing to inadequate health literacy. PWH and families are also exposed to a multitude of information sources via social media and traditional news channels, which often present incomplete, inaccurate, and contradictory content.^{15,16} Furthermore, in some countries, direct-to-patient marketing may present an additional confounder to patient comprehension, particularly in vulnerable groups.¹⁷ In addition to inadequate patient educational materials, a discordance often exists between the physician's perception of their patients' understanding and the patient's actual comprehension.^{14,18} This communication failure leads to postponement of treatment decision-making, non-adherence, and poorer health outcomes.¹⁴

Appropriate, individualized communication is necessary to facilitate targeted treatment approaches and disease prevention.¹⁹ This issue extends beyond patient understanding. Particularly, with emerging therapies and novel mechanisms of action, it is inappropriate to assume that HCPs have adequate understanding of gene therapy.

Proposed Solutions

A complementary approach includes patient centricity, defined as engaging with patients to achieve the best experience and outcomes for the individual and their family.¹³ The process of shared decision-making can reduce the information and knowledge imbalance, and lead to more personalized treatment decisions, better medical outcomes, treatment adherence, improved quality of life, and decreased costs of treatment and absenteeism.^{20–22} The introduction of a new option, such as gene therapy, provides opportunities for shared decision-making to ensure patients understand their best, individualized option.²² This type of patient-centric decision-making is relevant to clinical practice and is particularly important for AAV gene therapy due to current limitations on re-treatment via that modality. Importantly, shared decision-making is distinct from

informed consent, with a primary difference being the timing and extent of patient involvement.²³ Shared decision-making is more than a one-size-fits-all description of the risks and benefits associated with each treatment option in order to meet a legal requirement; patients, and family members where appropriate, should be actively involved in an individually tailored, two-way discussion with their care provider, with patient preferences and concerns at the forefront.²³

Appropriate Language in Patient Communication

A key element in a patient-centric approach is dialogue, which must be accessible to PWH and their families according to widely diverse levels of health and medical comprehension, as well as personal circumstances.^{13,18}

PWH who are diagnosed and treated, and families, tend to be well informed about their condition and are committed to its management, including keeping abreast of treatment options.²⁴ However, the evolving treatment landscape poses an array of questions, so it is imperative that PWH have access to health information that they can easily find, understand, and use to inform their decisions.

General recommendations to improve physician–patient communication include: avoiding assumptions of low or high patient health literacy, avoiding jargon and unnecessary detail, implementing the “teach-back” method (reiterating in your own words what was learned) to ensure full patient understanding, and preparing written materials, with only key points and graphics or other visuals where relevant.¹⁸ A recent review identified additional variables relevant to shared decision-making in hemophilia treatment, including bleeding phenotype, musculoskeletal status, treatment adherence, venous access, and lifestyle.³

When considering health literacy, it is also important to understand the issues facing PWH enrolling in clinical trials, and the clinical and technical terminologies involved. Physicians and the surrounding care team can play an important role in ensuring that patients achieve clinical trial literacy and are fully informed when making decisions about participation.²⁵ This is also necessary when communicating with patients who have already started their gene therapy journey in clinical practice,¹¹ who may still have outstanding questions or concerns.

The Q&A resource presented here will help to tailor communications and support a patient-centric shared decision-making process.

Aim

The Council of the Hemophilia Community (CHC) convened with the aim of filling an information gap through the development of a resource to support discussions between HCPs and PWH about gene therapy. Here, we summarize the results of focus group discussions conducted by the CHC, which aimed to define the patient journey in hemophilia gene therapy within the different life stages of PWH and create an accompanying Q&A resource for HCPs and PWH. The intention is to support shared decision-making in real-world practice by giving HCPs insight into likely patient questions regarding gene therapy and clinical trial participation.

Methods

Resource Development Strategy

The resources described here are based on expert discussions involving HCPs and patients. The CHC was established in 2019 as a multidisciplinary expert group, formed of independent advisors, HCPs, industry leads, and patient representatives with experience in medicine, research, advocacy, patient support, health economics, data, and healthcare access. The CHC collaborate on behalf of PWH to provide guidance for: 1) overcoming clinical and access challenges in the hemophilia environment; 2) perceived gaps in programs and initiatives; and 3) developing initiatives based on emerging insights.

Over the course of 3 roundtable meetings held between November 2020 and May 2021, the CHC first conducted a process of insight identification to understand the elements of the specific patient journey that could best guide the hemophilia community and facilitate treatment decision-making. The life cycle of PWH was aligned to patient journey stages, based on exchanges of opinion within the interdisciplinary working group. The CHC then identified and refined key

questions based on those defined in an early patient questionnaire and by the National Hemophilia Foundation (NHF).²⁶ The selection of these source materials was based on a consensus of expert opinion; no formal literature search was conducted.

Patient questions were then selected and assigned to the patient journey stages and refined by the CHC members during iterative CHC expert workstream discussions using a focus group format. Answers to the questions were refined separately by the authors following multiple rounds of review. The target audience for the developed questions and answers were hematologists and their patients.

Collaboration with Patients

This collaborative development and feedback process engaged all members of the CHC, patient groups, patient representatives, and nurses. In addition, both resources were reviewed by groups of European and US-based patients, caregivers, and parents of PWH (Bayer Global and European Patient Councils for Hemophilia) and the Bayer Hemophilia Employee Council, to seek their insight on the relevance and accessibility of the text, as well as their opinions on the need for any additional questions and answers. All members of the Bayer Global and European Patient Councils groups are PWH or a caregiver of a person with hemophilia. Members of the Bayer Hemophilia Council include Bayer employees with hemophilia. The resultant patient journey roadmap and Q&A resource were shared with the entire CHC for feedback. The authors met regularly to discuss this feedback, and to decide on the content and placement of key questions along the patient journey.

Results

The Patient Journey: Key Stages and Aims

As an initial step in developing the Q&A resource, the CHC undertook defining the patient journey through gene therapy for hemophilia. The CHC has categorized 5 pillars of the patient decision-making journey in the current treatment landscape:

- Pre-gene therapy information seeking
- Pre-gene therapy decision-making
- Treatment initiation
- Short-term post-gene therapy follow-up (≤ 1 year)
- Long-term post-gene therapy follow-up (> 1 year)

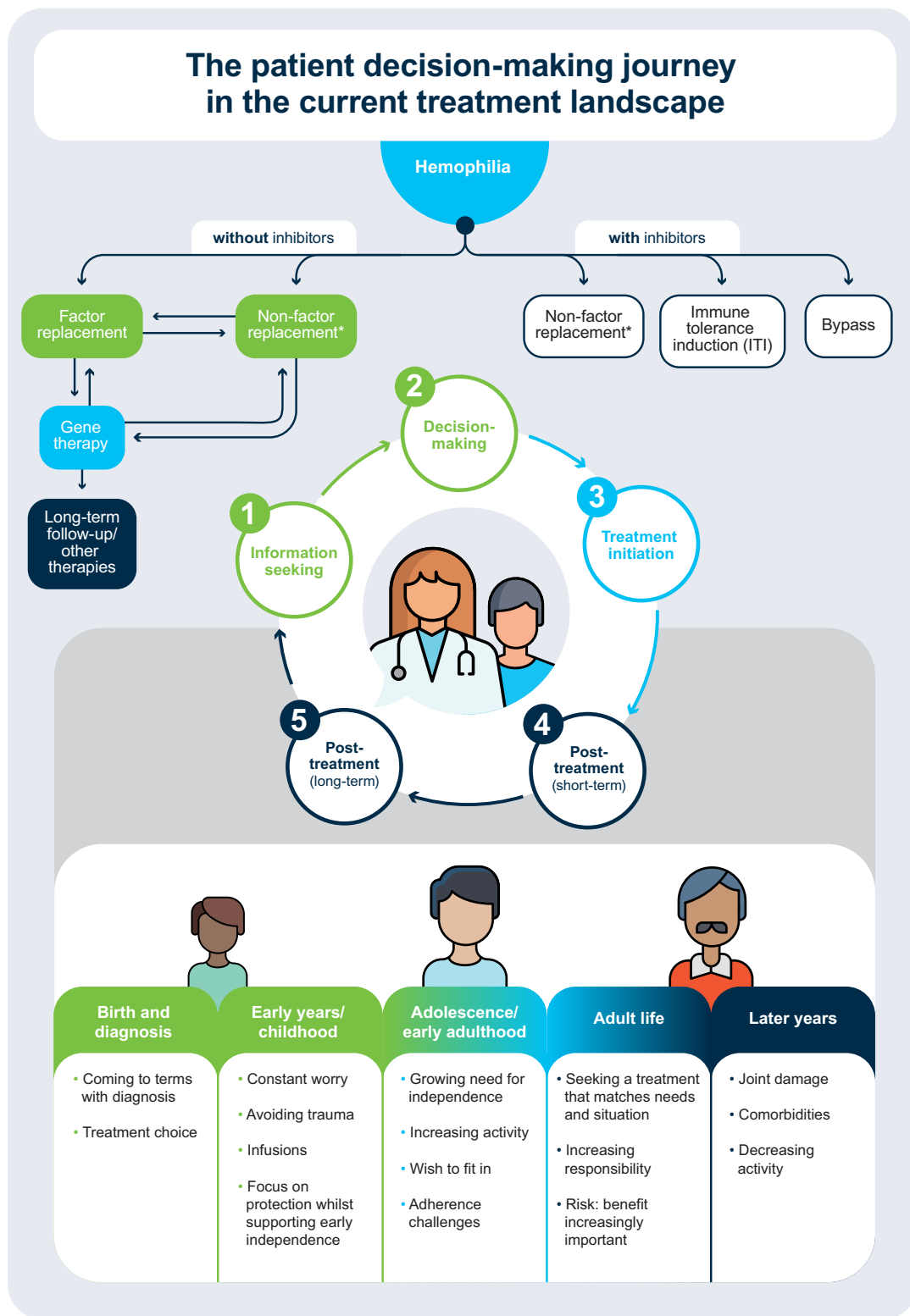
The patient journey as mapped onto these 5 pillars is shown in [Figure 1](#).

Key Themes of the Q&A Resource

The Q&A development process revealed several areas contributing to patient decision-making in hemophilia gene therapy. First, expectations of PWH need to be managed, as the potential benefits and risks of gene therapy are likely to vary among PWH. In addition, the need for a commitment to participating in a long-term registry^{21,27} should be communicated before gene therapy is initiated. Further explanations of eligibility and effects should be clarified, notably that any gene expression occurs only in somatic cells (not germline cells), hence any effect is not conveyed to future generations.²¹ The questions should also cover the current unknowns of treatment, including long-term durability, whether the achieved level of FVIII/FIX is sufficient to effectively prevent bleeds, and treatment options in the event that gene therapy does not achieve its therapeutic goals.

Summary of the Q&A Resource

The CHC agreed that questions from PWH concerning gene therapy tend to fall under the following broad categories: treatment regimen/adherence requirements, treatment predictability and variability, treatment durability, and the risk: benefit profile. The full, collated list of questions and answers is presented in the [Supplementary Materials](#). The resource is organized from initial information-seeking to decision-making, treatment initiation and trial information, and short- and



*Non-factor replacement is currently only available for hemophilia A

Figure 1 The patient decision-making journey.

long-term follow-up. The reading level of the document is a grade 10–11 (high school) level, based on a Flesch-Kincaid readability test. It is fully referenced, as appropriate, for further context and can serve as a practical tool for the treating physician in shared decision-making. Information to facilitate discussion regarding participation in clinical trials is also included, from eligibility through follow-up. Some of the questions deal with complex queries, such as explaining what gene therapy is and how it works in the body, as well as efficacy and safety.

Additional online resources to support patients considering gene therapy are summarized at the end of the [Supplementary Materials](#).

Discussion

Hemophilia Gene Therapy Awareness

The CHC-defined patient journey and Q&A resource reported here are designed to help to inform HCPs regarding the questions and considerations likely to be encountered by PWH at different life stages, and when discussing gene therapy options. Each patient's journey will encounter the emergence of new therapeutic options, growing evidence and evolving individual preferences, goals, aspirations, and risk tolerance.

By identifying and providing key information to aid these discussions on gene therapy, this tool will help to address knowledge gaps of HCPs and PWH. A recent global survey sent to patient organizations reported that although most (68%) PWH express that they have a basic understanding of gene therapy, only a small proportion (6%) consider themselves to have an advanced understanding.²⁸ A similar pattern was observed for HCPs, with 44% recording a basic or intermediate understanding, and only 12% reporting an advanced understanding.²⁸ A different international survey of physicians and scientists echoed these results, with 40% of physicians directly in hemophilia care claiming limited ability to discuss gene therapy with their patients.²⁹ As gene therapy emerges, it will be critical to meet the knowledge gaps of HCPs and PWH. Educating physicians, nurses, and the surrounding care teams who care for PWH will better enable them to meet the needs of their patients through constructive and informative discussions.²⁹ Although the majority of PWH report positive opinions of gene therapy, including with respect to such considerations as annual bleeding rates, factor levels, long-term impacts, use of factor replacement, and treatment costs,^{30–32} many believe that they will not benefit from new products (eg, gene therapy and new factor/non-factor replacement therapies).^{31,32} Therefore, HCPs will need to educate PWH about all available treatment options as they engage them in shared decision-making.³¹

HCP-Patient Communication on Gene Therapy Advances

The resources will be shareable during in-person or virtual consultations and available for reference afterwards. In order to maximize the impact of this tool, HCPs should become familiar with appropriate language and educational materials to answer these questions. Results from a qualitative study across a variety of stakeholders suggest that consistency in the language and terminology used when discussing hemophilia can reduce miscommunication and facilitate conversations, promoting informed decision-making. In particular, the need for appropriate terminology to describe gene therapy has been previously highlighted and that it is preferable to discuss “what gene therapy is,” rather than what current treatments “are not.”²⁴ As HCPs will likely become increasingly engaged in the use of gene therapy, their adoption and comfort with the preferred terminology will enhance their communications. The usefulness of the resource provided here should be evaluated by an assessment of publication metrics as well as focus group discussions to understand the uptake of the tool by the hemophilia community.

Lessons on communicating with patients may be learned from past and ongoing miscommunications between the scientific community and the public,³³ eg, the harmful misconceptions around antimicrobial resistance or those that arose from the flawed and ultimately retracted report of an association of the measles, mumps and rubella vaccine with autism development.^{34,35} Poorly delivered or incorrect information, including in clinical trials, can result in a lack of confidence in treatment, unnecessary costs, and discontinuity of care. Transparency is an essential criterion for gaining trust.³⁶ In particular, the need for adequate education of HCPs will be vital for facilitating these conversations, alongside the need to adjust the information and method of delivery to particular care contexts.

Strengths and Limitations

The Q&A resource provided here is a novel, readily available educational tool for HCPs and their patients. Its strengths include an easy-to-follow format, ready for use as a comprehensive shared decision-making resource in the clinic. Moreover, the development of the resource was heavily guided by its intended audience, therefore we hope it proves immediately useful.

The key limitation of the Q&A resource is its reading level (grade 10–11; high school), which is higher than the grade 5–8 level (10–14 years old) at which the average patient comfortably comprehends patient educational materials.^{37,38} However, this resource is intended for use by HCPs to tailor their delivery of the material appropriately to different patients (for example, by omitting or describing content based on patient knowledge and/or age) and thus the reading level is targeted higher to include relevant details. In addition, while the Q&A resource is intended to guide conversations with PWH, the patient journey starts in infancy and hence will also involve discussions with parents or other caregivers of pediatric patients, who may have additional specific questions. While gene therapy is not currently available to children, advice to parents of pediatric PWH should be provided to ensure full awareness of future considerations.³⁹ The Q&A resource therefore functions as a starting point from which HCPs can individualize discussions. Other concerns, including those of reimbursement and financing, while important, will vary by region and are beyond the scope of this article and Q&A resource. Clinical evaluations to date have been conducted predominantly in high-income countries,⁴⁰ and therefore, this communication tool is currently limited to patients in those regions. Finally, despite good levels of engagement across key stakeholder groups, the relatively small size and composition of the CHC group could limit the generalizability of these conclusions to the global hemophilia community.

Future Directions

Ideally, the resource would be updated and published as needed to provide the latest relevant information and address any feedback from the community. This work would benefit from even wider stakeholder engagement including surveying a larger, more diverse group of PWH. It would incorporate findings of clinical trials and other research (such as from registries) that would be of potential relevance to decision-making (eg, probability of expressing FVIII, levels of FVIII expression, duration of expression, probability of side effects) and shared and reviewed with patients as it becomes available.^{41–43}

Furthermore, while this resource provides an educational and decision support tool to aid discussions between HCPs and patients, barriers to providing requisite biomedical and clinical education about gene therapy for HCPs (eg, time and travel costs) should also be identified and addressed.²⁹

Conclusions and Key Takeaways

Gene therapy offers a potential alternative to lifelong infusions, with the promise of transformative changes in the lives of PWH^{7,44} and a major shift within the treatment paradigm.⁸ The emergence of gene therapy will also add to the complexity of treatment decisions faced by PWH and their families. HCPs will have a crucial role in providing the appropriate, personalized guidance and support to ensure that PWH fully understand the options available to them.

The educational and decision support resources described herein recognize that each patient's decision journey will evolve throughout their lifetime with their individual preferences at different life stages, and with the emergence of new therapies and a growing evidence base.

The Q&A resource provides HCPs and PWH with timely, relevant information, facilitates discussions, and empowers PWH to engage in shared decision-making. As gene therapy products enter the market, the themes and questions mapped here should stimulate discussion and aid interactions among HCPs, PWH, and family members, to ensure that they are fully informed and realize the clinical potential of this treatment. While the issues discussed here pertain to hemophilia, they could also be applied to other hereditary diseases with multiple treatment options.

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