Received: 5 November 2024 | Revised: 24 January 2025 | Accepted: 19 February 2025

https://doi.org/10.1016/j.rpth.2025.102710

ORIGINAL ARTICLE

Development of a novel gene editing lexicon for hemophilia: methodology and results

Craig M. Kessler[1] | Leonard A. Valentino[2,3] | Courtney D. Thornburg[4,5] | Carmen Unzu[6] | Mark A. Kay[7] | Flora Peyvandi[8] | Penni Smith[9] | Wolfgang Miesbach[10] | William McKeown[11] | Glenn F. Pierce[12] | Kate Khair[13] | Katarina Starcevic[14] | Monisha Pillai[14] | Micheala Jones[15] | Anil Sindhurakar[15] | Lauren Whyte[15] | Virginie Delwart[15] | Megan Chiao[15] | David E. Gutstein[15] | Ilia Antonino[16] | Cedric Hermans[17] | Steven W. Pipe[18]

[1]Georgetown University, Washington, DC, USA

[2]National Bleeding Disorders Foundation, New York City, New York, USA

[3]Rush University, Chicago, Illinois, USA

[4]University of California San Diego, La Jolla, California, USA

[5]Rady Children's Hospital-San Diego, San Diego, California, USA

[6]DNA and RNA Medicine Division, Cima Universidad de Navarra, Instituto de Investigación Sanitaria de Navarra, Pamplona, Spain

[7]Stanford University, Palo Alto, California, USA

[8]University of Milan, Milan, Italy

[9]Utah Center for Bleeding and Clotting Disorders, Salt Lake City, Utah, USA

[10]University Hospital Frankfurt, Frankfurt, Germany

[11]Care of Elderly Medicine, Antrim Area Hospital, Antrim, United Kingdom

[12]World Federation of Hemophilia, Montreal, Québec, Canada

[13]Haemnet, London, United Kingdom

[14]Maslansky and Partners, New York City, New York, USA

[15]Regeneron Pharmaceuticals, Inc., Tarrytown, New York, USA

[16]Intellia Therapeutics, Inc., Cambridge, Massachusetts, USA

[17]Saint-Luc University Hospital, Brussels, Belgium

[18]University of Michigan, Ann Arbor, Michigan, USA

Correspondence
Craig M. Kessler, Georgetown University Medical Center, Washington, DC 20007-2197, USA.
Email: KESSLERC@gunet.georgetown.edu

Handling Editor: Dr Johnny Mahlangu

Abstract

Background: Clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein 9 (Cas9)-based targeted gene editing platforms are being developed to treat genetic diseases like hemophilia. Such novel therapy involves complex concepts and terminology that require aligned language to engage key stakeholders in the hemophilia community. Thus, a globally aligned gene editing lexicon – a consistent language to communicate the fundamentals of gene editing in hemophilia, designed to be credible and accessible for people with hemophilia and caregivers while avoiding unnecessary complexity – is required to address this need.

Objectives: To establish an aligned language and communications framework that facilitates informed consent and shared decision-making regarding gene editing and treatment considerations in hemophilia.

Methods: Through an innovative partnership with global experts in hemophilia, gene editing, and biotechnology, initial insights were gathered via interviews, workshops, and analysis of existing language within the hemophilia community. Qualitative research involving lived experience experts (people with hemophilia and caregivers; $n = 43$) and hematologists ($n = 24$) informed the lexicon development, which was further validated by a steering committee of global experts in the hemophilia and gene editing fields. Finally, optimized language recommendations were developed for a clear, consistent gene editing lexicon.

Results: Key themes included insights into audience mindsets, guiding language principles, and optimized terminology for key topics like gene editing concepts and post-treatment considerations. Audience mindsets revealed cautious optimism around gene therapy, with more skepticism around gene editing. Guiding language principles indicated a preference for plainspoken over technical language, definitions that link to patient benefits, and explanations that highlight the precise nature of gene editing.

Conclusion: This collaborative approach ensures broad adoption of the lexicon within the hemophilia community and readiness for beta testing.

KEYWORDS

blood coagulation disorders, clustered regularly interspaced short palindromic repeats, gene editing, hemophilia A, hemophilia B, lexicon

Essentials

- CRISPR-Cas9–based gene editing is an emerging therapy for hemophilia involving complex vocabulary.
- A gene editing lexicon was developed with guidance from hemophilia and gene editing experts.
- Optimized language recommendations were developed for a clear, consistent gene editing lexicon.
- The novel collaborative, community-based approach supports the successful adoption of this lexicon.

1 | INTRODUCTION

Hemophilia is a genetic disorder characterized by coagulation factor deficiency [1,2]. It is caused by a genetic mutation in the long arm of the X chromosome [3]. Recent advances in treatment for hemophilia, with the availability of subcutaneous nonreplacement therapies, changed the approach to prophylaxis of bleeding, even in children with hemophilia [4,5]. Despite these advances, current treatment options for people with hemophilia can be associated with high treatment and financial burdens on individuals and healthcare systems [6]. In addition, although younger patients on prophylaxis treatment with extended half-life factor therapeutics experience fewer episodes of hemarthrosis [7], patients with moderate to severe hemophilia who are treated with clotting factor concentrates continue to experience breakthrough bleeds and joint diseases potentially due to lack of steady-state factor and hemostatic levels [1,2,8]. Given the challenges associated with current treatments for hemophilia, novel treatment modalities are in development [8]. Clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein 9 (Cas9)–based gene editing platforms represent one such emerging treatment option. These platforms have the potential to address the unmet needs of the hemophilia community [9–11].

One of the challenges associated with implementing novel and advanced treatment options like gene editing platforms is that they involve complex concepts and terminologies that are not familiar within the hemophilia community. For instance, it may not be clear to the hemophilia audience that CRISPR-based gene insertion targets liver cells, which are nonreproductive cells, and therefore, its effects cannot be passed down to future generations. In addition, the language used to explain and discuss gene editing is also not aligned across key audiences: lived experience experts [12] (LEEs; people with hemophilia and their families and caregivers), healthcare professionals (HCPs), people with hemophilia advocacy groups, regulatory agencies, and payors. This makes it difficult to facilitate shared decision-making between HCPs and people considering gene editing, which is a major barrier to achieving truly informed consent. An aligned language for such novel therapeutic

technologies is therefore critical for improving understanding among the hemophilia community and achieving informed consent.

Here, we report the development of a globally aligned gene editing lexicon – one that is credible and easily understood by people with hemophilia and the hemophilia community. Lexicon development used an innovative approach involving close partnerships among hemophilia, gene and cell therapy, and biotechnology organizations. Insights were gathered through in-depth interviews, language audits, workshops, and qualitative research across the United States of America, the United Kingdom, and Germany with LEEs and hematologists. The lexicon was finalized following input from a lexicon steering committee composed of global experts from leading scientific and patient organizations in the hemophilia and gene editing fields. The major goal of this lexicon was to establish a clear and consistent common language and communications framework that facilitates informed consent and shared decision-making regarding gene editing and treatment considerations in hemophilia.

2 | METHODS

2.1 | Study design and setting

This study, conducted between August 2023 and January 2024, used a 7-stage cumulative approach. Stages 1 to 3 have been completed, where preliminary insights were gathered through an audit of language to describe genetic treatments in hemophilia and interactions with leading representatives in the field [13]. These initial stages laid the groundwork for stages 4 to 7, outlined and described in further detail below.

- Stage 4: development of discrete language stimuli.
- Stage 5: qualitative lexicon research involving online group interviews with hemophilia community stakeholders in the United States of America, United Kingdom, and Germany.
- Stage 6: a review and refinement stage with the lexicon steering committee.
- Stage 7: a language strategy involving recommendations for a foundational gene editing lexicon in hemophilia.

2.2 | Participant selection and study procedures

The comprehensive, multistep approach to lexicon development is outlined in Figure 1 and described in further detail below.

2.2.1 | Stage 1: language landscape analysis

An in-depth audit was conducted, including a comparative analysis of the public-facing language used to describe genetic treatments in hemophilia across 3 patient advocacy groups and 1 scientific organization (National Bleeding Disorders Foundation, formerly NHF; European Haemophilia Consortium; World Federation of Hemophilia; International Society on Thrombosis and Haemostasis). All were chosen based on their legacy and influence in the hemophilia field. Findings were used to understand key communication topics and established vocabulary to

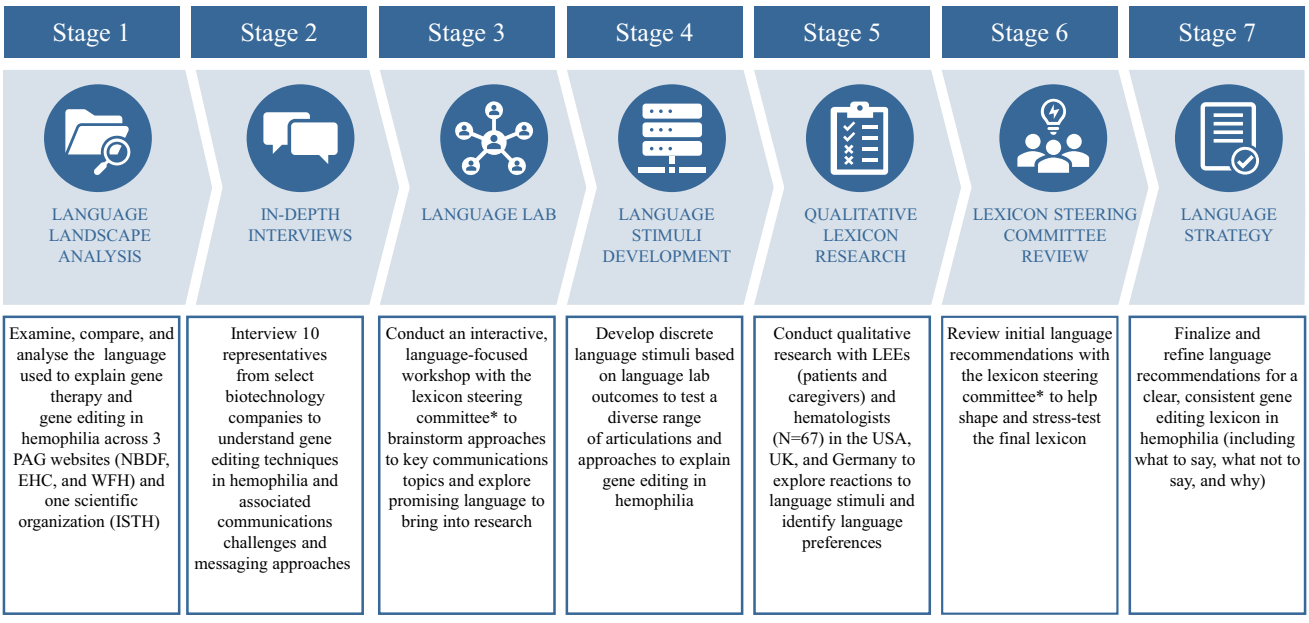

FIGURE 1 Stages of lexicon development. *The lexicon steering committee is composed of global experts from leading scientific and patient organizations in the hemophilia and gene editing fields.

EHC, European Haemophilia Consortium; ISTH, International Society on Thrombosis and Haemostasis; LEE, lived experience expert; NBDF, National Bleeding Disorders Foundation; PAG, patient advocacy group; UK, United Kingdom; USA, United States of America; WFH, World Federation of Hemophilia.

explain genetic treatments in hemophilia. Findings were also used to develop a comprehensive discussion guide for stage 2.

2.2.2 | Stage 2: in-depth interviews

Five in-depth interviews were conducted with representatives from select biotechnology companies ($N = 10$) to understand gene editing techniques in hemophilia and associated communication challenges and uncover key anticipated questions. These 60-minute virtual interviews were led by market research professionals specializing in language strategy. Findings were used to develop a workshop curriculum for stage 3.

Participants were chosen based on their in-depth knowledge of current and novel gene editing technologies, involvement and experience in developing and implementing such technologies, and knowledge of the hemophilia community, including people with hemophilia and patient advocates.

2.2.3 | Stage 3: language laboratory

An interactive language-focused workshop was conducted with the lexicon steering committee (composed of 11 global experts from leading scientific and patient organizations in the hemophilia and gene editing fields) to discuss common patient attitudes on gene editing, brainstorm approaches to key communication topics, and explore promising language to bring into research. Experts also answered a series of open-ended questions to explore how they articulate, visualize, and conceptualize gene editing techniques and their application in hemophilia in advance of the workshop. Findings were used to develop discrete language stimuli in stage 4.

2.2.4 | Stage 4: language stimuli development

To evaluate articulations and approaches for explaining gene editing in hemophilia, 13 sets of discrete language stimuli spanning 8 key topics were developed, modeled on a frequently asked question structure (ie, each language articulation was designed as a response to a key question). Stimuli spanned 3 main sections, reflecting a critical building block for understanding gene editing in hemophilia. Stimuli also included forced-choice poll questions to quantify reactions and preferences for specific pieces of language. This approach helped participants understand the general principles of gene editing before delving into the details of more novel technologies (specifically, CRISPR-Cas9 gene insertion technology). Each set of stimuli fell into 1 of 3 major themes: introduction to gene editing, introduction to CRISPR-based gene insertion, and addressing potential concerns. The full set of stimuli topics is shown in Table 1.

TABLE 1 Stimuli topics for qualitative discussion.

Introduction to gene editing	
1.	What is gene editing?
2.	How can we describe gene editing more visually?
Introduction to CRISPR-based gene insertion	
3.	What is the goal of gene insertion in hemophilia?
4.	How does CRISPR-based gene insertion work?
5.	How is genetic material delivered?
Addressing potential concerns	
6.	Can the effects of CRISPR-based gene insertion be inherited?
7.	Can I get CRISPR-based gene insertion more than once?
8.	What does follow-up look like?

CRISPR, clustered regularly interspaced short palindromic repeats.

2.2.5 | Stage 5: qualitative lexicon research

To evaluate language concepts for clarity, comprehension, and credibility, 11 qualitative research sessions (Supplementary Table S1), each 135 minutes long, were held with participants ($N = 67$) across 3 markets (the United States of America, United Kingdom, and Germany), including LEEs and hematologists (Table 2). Here, stimuli from stage 4 were explored in detail in group sessions with participants, each led by an independent moderator. Feedback was collected through forced-choice poll questions and group discussion using planned and spontaneous prompts and questioning. Participants were encouraged to share their candid personal opinions. Feedback was used to develop insights into audience mindsets, guiding lexicon principles, and specific language recommendations for use in definitions, descriptions, and explanations of novel gene editing techniques and related patient considerations.

Participants in stage 5 were intended to be representative of the hemophilia community. Structured screener interviews were used to confirm eligibility based on criteria detailed in Table 3 [14] and to ensure a diverse set of participants from across the United States of America, United Kingdom, and Germany and audiences (LEEs and hematologists). A total of 24 hematologists and 43 LEEs met the eligibility criteria for participation in stage 5. Among hematologists, 50% (12/24) treated adult people with hemophilia only and practiced across a diversity of locations (hemophilia treatment centers, hemophilia comprehensive care centers, nonhemophilia treatment center community hospitals, nonhemophilia treatment center academic/university hospitals, and private practices). Patients represented a population likely to be eligible for future gene editing treatments. Of 23 LEEs (people with hemophilia), 56.5% (13/23) had hemophilia A, and the remaining 43.5% (10/23) had hemophilia B. Of 20 LEEs (caregivers), 60% (12/20) provided care for people with hemophilia A and 40% (8/20) provided care for people with hemophilia B; 90% (18/20) provided care for people with hemophilia aged >18 years and 10% (2/20) provided care for children with hemophilia aged 8 to 17 years (Table 2).

2.2.6 | Stage 6: lexicon steering committee review

Preliminary research results and initial language recommendations were reviewed by the lexicon steering committee to finalize the lexicon.

TABLE 2 Qualitative research participants.

Participants	United States of America (*n* = 27)	United Kingdom (*n* = 19)	Germany[b] (*n* = 21)
HCPs[a]	Hematologists (*n* = 10) • Treat people with moderate to severe hem A or B (*n* = 10) ○ Treat adult people with hemophilia only (*n* = 7) ○ Treat both adult and pediatric people with hemophilia (*n* = 3)	Hematologists (*n* = 6) • Treat people with moderate to severe hem A or B (*n* = 6) ○ Treat adult people with hemophilia only (*n* = 3) ○ Treat both adult and pediatric people with hemophilia (*n* = 3)	Hematologists (*n* = 8) • Treat people with moderate to severe hem A or B (*n* = 8) ○ Treat adult people with hemophilia only (*n* = 2) ○ Treat both adult and pediatric people with hemophilia (*n* = 6)
LEEs (people with hemophilia)	LEEs (*n* = 10) • Male (*n* = 9) • Race/ethnicity[c] ○ Caucasian/White (*n* = 5) ○ Caucasian/White, Hispanic/Latino (*n* = 2) ○ Black/African American (*n* = 2) ○ Asian/Pacific Islander (*n* = 1) • Hem A (*n* = 3) ○ Moderate (*n* = 2) ○ Severe (*n* = 1) • Hem B (*n* = 7) ○ Moderate (*n* = 2) ○ Severe (*n* = 5)	LEEs (*n* = 7) • Male (*n* = 7) • Race/ethnicity[c] ○ Caucasian/White (*n* = 7) • Hem A (*n* = 5) ○ Moderate (*n* = 3) ○ Severe (*n* = 2) • Hem B (*n* = 2) ○ Severe (*n* = 2)	LEEs (*n* = 6) • Male (*n* = 6) • Hem A (*n* = 5) ○ Moderate (*n* = 1) ○ Severe (*n* = 4) • Hem B (*n* = 1) ○ Moderate (*n* = 1)
LEEs (caregivers)	LEEs (*n* = 7) • Race/ethnicity[c] ○ Caucasian/White (*n* = 3) ○ Hispanic/Latino (*n* = 1) ○ Black/African American (*n* = 3) • Care for people with hem B (*n* = 7) ○ Moderate (*n* = 1) ○ Severe (*n* = 6) • Care for people with hemophilia aged <18 y (*n* = 5)	LEEs (*n* = 6) • Race/ethnicity[c] ○ Caucasian/White (*n* = 6) • Care for people with hem A (*n* = 5) ○ Severe (*n* = 5) • Care for people with hem B (*n* = 1) ○ Severe (*n* = 1) • Care for people with hemophilia aged <18 y (*n* = 6)	LEEs (*n* = 7) • Care for people with hem A (*n* = 7) ○ Moderate (*n* = 3) ○ Severe (*n* = 4) • Care for people with hemophilia aged <18 y (*n* = 7)

HCP, healthcare professionals; Hem, hemophilia; LEE, lived experience experts.
[a]For specialty audiences like HCPs, ethnicity was not part of the screening criteria.
[b]Due to stricter privacy laws in the European Union, ethnicity data were not collected.
[c]Respondents could select as many race/ethnicity categories as they felt best described them.

2.2.7 | Stage 7: language strategy

Optimized language recommendations for a clear, consistent gene editing lexicon in hemophilia were built based on analysis of the findings from stages 1 to 6. The lexicon included insights into audience mindsets, communication context and guardrails, and considerations for adapting language based on audience literacy levels, market and audience-specific nuances, and the future evolution of the technology.

2.3 | Analyses

Results were derived qualitatively through in-depth analysis and synthesis of respondents' reactions to language based on clarity, comprehension, and credibility, as well as through quantitative analysis of results from forced-choice polling exercises. To develop a lexicon with the broadest application, priority was given to findings relevant across most audiences and markets. Following feedback and refinement from the lexicon steering committee, optimized language recommendations were developed for a clear, consistent gene editing lexicon.

2.4 | Ethical approval

This study was approved by the relevant institutional review boards and ethics committees.

3 | RESULTS

Results from the initial stages (1-3) revealed a critical need for a simple, clear, and consistent lexicon to explain gene editing in hemophilia to enable informed consent and decision-making when it comes to treatment considerations. The detailed outcomes of the initial stages were published separately [13].

TABLE 3 Eligibility criteria for qualitative research session participation.

Hematologists	• Actively involved[a] in directly treating an adequate proportion[b] of people with moderate to severe[c] hemophilia • At least 50% of their patients receive prophylaxis treatment with factor replacement therapy • Open to considering gene therapy for people with hemophilia
Patients	• Aged 18 to 65 y • Diagnosed with moderate to severe[c] hemophilia A or B • Currently using a factor replacement product as the primary treatment on an on-demand or prophylactic dosing schedule • Open to considering gene therapy as a future treatment • Have not previously participated in a gene therapy clinical trial
Caregivers	• Primarily nonprofessional caregivers to an individual with moderate to severe[c] hemophilia A or B • The individual they care for has not previously participated in a gene therapy clinical trial

[a]Defined as comprising at least 50% of their working hours.
[b]Defined as treating at least 25% of the total number of patients treated.
[c]Moderate is defined as factor levels at 1% to 5%, and severe is defined as factor levels <1% [14].

Insights from the qualitative lexicon research and refinement (stages 5 and 6) fell into 3 key themes: stakeholder mindsets, guiding language principles, and optimized lexicon recommendations for key topics.

3.1 | Stakeholder mindsets

Results showed that the terms "gene therapy" and "gene editing" evoke different associations. Where gene therapy was associated with curative potential, gene editing was associated with "science fiction" and ethical concerns. Although there was a level of skepticism when discussing the therapeutic application of both techniques, there was more cautious optimism around gene therapy and more doubt around gene editing. Results also indicated confusion about the differences between each technique (Supplementary Table S2).

3.2 | Guiding language principles

Findings indicated a preference for language adhering to the below core principles (Supplementary Table S3):

- Plainspoken language over technical language
- Definitions linked to patient benefits
- Finding the right balance of detail – not too little or too much

Explanations anchored in precision to build confidence in the face of novelty and skepticism. These overarching principles guided the refinement of specific lexicon recommendations across topics.

3.3 | Lexicon recommendations for key topics

The key topics on which to build and optimize language were identified during the initial phases and defined in stage 4. These included definitions and descriptions of gene editing and gene insertion/novel gene insertion techniques, and messaging around issues like post-treatment follow-up, scientific unknowns, and inheritance (ie, language that distinguishes between episomal and somatic genetic treatments and clarifies whether the effects of treatment are passed down to children).

3.3.1 | Explaining gene editing

When describing gene editing, there was a preference for the term "medical technology." Although audiences saw its potential to become a treatment, the word "treatment" implies something that is ready for use, which hematologists reject, given its trial status and lack of long-term evidence. "Technology" alone communicates something novel, untested, and scary. "Medical technology," however, is more credible, capturing that gene editing is an evolving scientific advancement with direct health benefits (Figure 2; [15]).

Plainspoken, descriptive definitions of gene editing were preferable to help audiences visualize the changes it can make while avoiding the unease that comes with scientific jargon. However, what was considered "plainspoken" differed by the audience – there was a need to balance simplicity with sufficient detail when describing what "editing" entails. For hematologists, that meant characterizing gene editing as "a medical technology that is used to inactivate harmful genes, add missing ones, or repair faulty ones." For people with hemophilia, that meant describing gene editing as "a medical technology that is used to fix, add, or turn off genes," using familiar language to break down possible "edits" into specific actions (Figure 2; Supplementary Table S4).

Metaphorical descriptions can help audiences better visualize how gene editing works but must avoid oversimplification and be centered on precision. For example, metaphors comparing gene editing to copyediting written language resonated, whereas metaphors comparing it to adapting a cake recipe were rejected (Supplementary Figure S1; Supplementary Table S5).

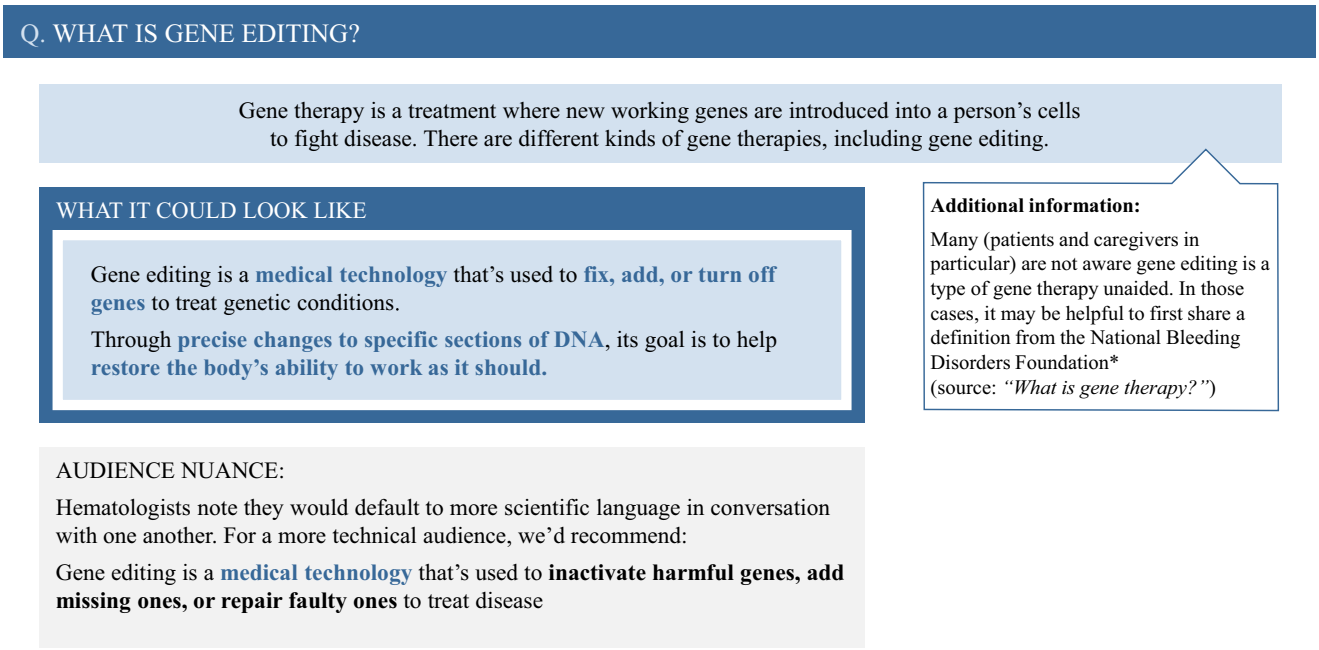

FIGURE 2 Explaining gene editing. *National Bleeding Disorders Foundation [15].

When describing how gene editing works, leaning into precision to connote a more targeted, intentional level of change helped reassure people with hemophilia that only what is necessary will be altered. In describing what gene editing does, anchoring to the end goal – the benefit to people with hemophilia – gave audiences a reason to keep listening despite skepticism and clarified the value and potential of gene editing.

For visual descriptions, there was a preference for comparing genes to a "series of letters" (Supplementary Figure S1; Supplementary Table S5). It is a familiar construct to many people with hemophilia, and it is close to how hematologists understand DNA – as a series of letters or base pairs. Across markets, the precision implied by fixing a piece of language resonated, and metaphors implying an exact degree of change – "like fixing a typo" – can enhance comfort and communicate how a small change can make a big difference.

3.3.2 | Explaining novel gene insertion methods

When describing the cause of hemophilia, audiences preferred the phrase "genetic mutation," which is considered familiar, scientifically accurate, and neutral.

However, some audiences – people with hemophilia in the United Kingdom and hematologists in the European Union (United Kingdom and Germany) – push back on the phrase "genetic mutation." In the United Kingdom, people with hemophilia tend to think of hemophilia as an issue of low protein or factor levels rather than a genetic issue. For European Union hematologists, there is debate around concerns that "mutation" risks faulting people with hemophilia. Overall, most European Union hematologists conclude that scientifically accurate terms like "genetic mutation" drive better understanding for everyone, regardless of sensitivities. In contrast, the term "genetic error" is rejected across markets and audiences for both being inaccurate and placing undue blame on people with hemophilia.

When describing the goal of gene insertion, "independent" factor production resonated. Although hemophilia is understood as a genetic condition, it is experienced as a dependence on factor replacement, and people with hemophilia are drawn to solutions that "enable the body to produce clotting factor ***on its own.***" However, more absolute, definitive language, like claims to "*eliminate*" the need for factor replacement altogether, triggered skepticism when presented without sufficient evidence (Supplementary Figure S2; Supplementary Table S6).

When explaining novel CRISPR-Cas9–based gene insertion, precision through the concept of "targeted" gene insertion improved confidence (Supplementary Figure S3; Supplementary Table S7) and encompassed how the technique differs from and builds on prior approaches. A plainspoken "2-step" breakdown also helped LEEs understand the technique by dividing it into simple, digestible parts. Similarly, a "2-part" breakdown of CRISPR helped visualize the concepts. It was noted that each major component of CRISPR (Cas9 and guide RNA) must be defined upon introduction. Audiences also noted the value of metaphorical descriptions, particularly comparing the technology to a "shipping and delivery" construct, although it must be presented alongside a robust technical definition to improve confidence.

Another critical consideration for explaining gene insertion included closing with a benefit that draws a clear link between the technical treatment details and the real-world outcome for people with hemophilia. Connecting to a benefit with an immediate and direct impact on patients' daily lives (ie, alleviating the burden of factor replacement therapy) is especially resonant.

When discussing gene insertion methods with hematologists, it was crucial to mention the *in vivo* nature, as hematologists consider it a valuable advancement in the gene editing field. This distinction was especially important given that gene editing techniques can vary by therapeutic area. For instance, recently approved gene editing therapy for β-thalassemia and sickle cell anemia is *ex vivo* in nature [16]. The term was less valuable for LEEs who are not familiar with it (or its difference from *ex vivo* techniques).

In explaining the delivery of genetic material, LEEs indicated a preference for straightforward scientific explanations that close with reassurance (Supplementary Figure S4; Supplementary Table S8). People with hemophilia are not inherently fearful of "viral" vectors, given their use in vaccines, but they prefer scientific terms over metaphorical descriptions like "delivery vehicle," which sound like attempts to sugarcoat information. However, explaining how the virus is changed helps alleviate worries about the risk of viral infection, and the use of "therapeutic" gene assures the positive health benefit of what is delivered. Similarly, explaining why a virus is used provides a helpful window into the scientific rationale behind the approach, providing reassurance. Finally, using "can't" (implying it cannot cause disease) adds an extra layer of reassurance in being more definitive than a word like "won't."

3.3.3 | Addressing potential concerns

The most urgent concerns of people with hemophilia were about inheritance and follow-up (Supplementary Figure S5; Supplementary Table S9). For these topics, plainspoken biological definitions and definitive language work best. Audiences do not need definitions of somatic and germ cells – or eggs and sperm – to understand. They prefer more literal explanations that leave less room for misinterpretation, like "[treatment affects] nonreproductive cells" and "[the effects] can't be passed down."

When describing follow-up, characterizing the treatment as "a one-time therapy" was a simple, neutral way to acknowledge permanence and irreversibility (Supplementary Figure S6; Supplementary Table S10). Further, explaining *why* it is currently a one-time treatment aided understanding; people with hemophilia are familiar with the idea of immune responses and antibodies (particularly considering coronavirus disease 2019) and appreciate the scientific explanation behind the real-world implications. There was also a need for reassurance around backup options. People with hemophilia often wonder if they can return to factor replacement therapy after genetic treatment, and the option to revert to baseline is crucial for making an informed treatment decision.

Another important concern was the scientific unknowns of treatment. Here, candid language builds credibility and trust. However, the order matters – language should lead with the knowns, acknowledge the unknowns, and close with reassurance on active efforts to push knowledge forward. Anchoring to what is known gives people with hemophilia a reason to consider treatment. Active efforts to advance knowledge inspire optimism and reassure people with hemophilia that this is a rigorous, scientifically validated treatment approach that will only continue to advance. In contrast, leading with acknowledgments about unanswered questions and effects that cannot be measured risks intimidating people with hemophilia. It is best to acknowledge the unknowns only after stating what is known.

In summary, neutral but honest language helps avoid unnecessary alarm. For example, "lifelong follow-up" can sound like a heavy burden, whereas "regular follow-up" is still accurate while sounding more manageable and familiar to people with hemophilia, given their current treatment regimens (Supplementary Figure S7; Supplementary Table S11).

4 | DISCUSSION

New and increasingly complex technologies are changing the hemophilia treatment landscape, making new ambitions – including the possibility of a cure – attainable [17,18]. To successfully implement such technologies, there must be an aligned language used by all stakeholders. Results show that a clear, consistent, and globally aligned lexicon for novel therapeutic platforms like gene editing can help build understanding and awareness among the hemophilia community. Further, outcomes suggest that the use of preferred language can increase comfort during discussions of novel treatments and related considerations [19,20].

Literature indicates the need for sources of clear, reliable information to weigh the risks and benefits of potential new gene therapies from physician, patient, and caregiver perspectives [21–23]. Moreover, studies like this suggest that consistent use of a community-informed lexicon can minimize miscommunication and facilitate informed decision-making regarding treatment opportunities and choices [21]. Therefore, there is a need to balance the depth of information with the existing knowledge and sensitivities of people with hemophilia, as well as levels of existing doubt and skepticism.

Through this initiative, several key lessons emerged. First, fostering collaborative partnerships between LEEs, HCPs, and researchers proved paramount in creating patient-centered communications that accurately reflect the diverse experiences within the hemophilia community. It also engendered a sense of ownership and inclusivity among all stakeholders, allowing them to advocate for themselves and others with authenticity and empathy. Moreover, communicating highly technical concepts in plainspoken yet descriptive language ensures accessibility across individuals of various backgrounds and education levels. Finally, the iterative nature of lexicon development highlighted the need for further refinement based on evolving needs and advances in technology to ensure its continual relevance and future impact.

Key limitations of this study include its qualitative nature, the focus on English and German languages, a lack of participants from the wider hemophilia care team, and difficulty anticipating future scientific advances. To supplement the findings of this study, future studies could incorporate a more global scale of participants, including a holistic hemophilia care treatment team. They may also incorporate a

quantitative approach to lexicon preferences, delve deeper into topics like potential side effects of gene therapy in children given that gene therapies approved so far have been in adults, and explore differences in subgroups like between those with moderate and severe hemophilia and those with hemophilia A and hemophilia B. In addition, it might be beneficial to focus on expanding the application of the lexicon beyond hemophilia to other genetic disorders. The collaborative, community-based approach of this study makes it particularly well-suited for beta testing, audience-appropriate modifications, and wider adoption.

The outcomes of this study provide a strong foundation for a novel gene editing lexicon. Consistent use of globally aligned language is instrumental in building a united hemophilia community that is well-informed about the risks, benefits, and considerations of novel treatment options like gene editing. Insights into stakeholder mindsets, guiding language principles, and optimized language for key topics outlined here could be instrumental in future adaptations of the lexicon as social norms, cultural trends, and scientific discoveries evolve alongside it.

ACKNOWLEDGMENTS

The authors thank the patients, caregivers, and their family members involved in this study. The authors also thank Amy L. Dunn for her contributions to the initial stages of lexicon development. Editorial support was provided by Oberon, OPEN Health Communications (London, United Kingdom), and funded by Regeneron Pharmaceuticals, Inc, in accordance with Good Publication Practice (GPP; https://www.ismpp.org/gpp-2022).

FUNDING

This study was funded by Regeneron Pharmaceuticals, Inc, and Intellia Therapeutics, Inc. The sponsor was involved in the study design and data collection, analysis, and interpretation, as well as data checking of results described in the manuscript. The authors had unrestricted access to the study data, were responsible for all content and editorial decisions, and received no honoraria related to the development of this publication.

AUTHOR CONTRIBUTIONS

C.M.K., M.J., and C.H. were involved with conceptualization; C.D.T., W. McKeown, and M.J. were involved with data interpretation; G.F.P. and M.J. were involved with data collection and/or analysis; K.S. and M.P. were involved with the developing the methodology; M.J. was involved with the study design; C.M.K., L.A.V., C.D.T., C.U., M.A.K., F.P., P.S., W. Miesbach, W. McKeown, G.F.P., K.K., K.S., M.P., M.J., A.S., L.W., V.D., M.C., D.E.G., I.A., C.H., and S.W.P. were involved with writing (review and editing).

RELATIONSHIP DISCLOSURE

C.M.K.: grants/research support from Bayer, Genentech, Octapharma, and Regeneron Pharmaceuticals, Inc; consulting fees from Bayer, Biogen, BioMarin Pharmaceutical, CSL, Genentech, Novo Nordisk, Octapharma, Pfizer, and Takeda; participation in a data and safety monitoring board for Bayer and Octapharma. L.A.V.: former president and chief executive officer of the National Bleeding Disorders Foundation. C.D.T.: grants to the institution from the American Thrombosis and Hemostasis Network, BioMarin Pharmaceutical, Inc, and Novo Nordisk; consulting fees from CSL Behring, Genentech, Pfizer, Regeneron Pharmaceuticals, Inc, and Sanofi; honoraria for an educational event from Spark Therapeutics and for manuscript writing from Wiley Publishing; support for attending meetings and/or travel from the American Thrombosis and Hemostasis Network and National Bleeding Disorders Foundation; unpaid leadership or fiduciary role in a study group steering committee for the American Thrombosis and Hemostasis Network and in a medical and scientific advisory board for the National Bleeding Disorders Foundation. C.U.: grant from Pfizer Global Medical Grants competitive grant program; consulting fees from Regeneron Pharmaceuticals, Inc. M.A.K.: role as principal investigator for the study described in the present manuscript supported by grant R01 HL064274, paid to the institution; consulting fees from Regeneron Pharmaceuticals, Inc. F.P.: payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from Spark Therapeutics and Takeda. Participation on a Data Safety Monitoring Board or Advisory Board for BioMarin Pharmaceutical, Inc, CSL Behring, Roche, Sanofi, Sobi, and Regeneron Pharmaceuticals, Inc. P.S.: support for participation in the lexicon steering committee for the study described in the present manuscript from Regeneron Pharmaceuticals, Inc. W.M.: research support from Bayer, Biotest, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, Sanofi, and Takeda/Shire; travel support from Bayer, BioMarin Pharmaceutical, Inc, Biotest, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Takeda/Shire, and UniQure; speakers bureau for Bayer, BioMarin Pharmaceutical, Inc, Biotest, CSL Behring, Chugai, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, and Takeda/Shire; scientific advisory board for Bayer, BioMarin Pharmaceutical, Inc, Biotest, CSL Behring, Chugai, Freeline, LFB, Novo Nordisk, Octapharma, Pfizer, Regeneron Pharmaceuticals, Inc, Roche, Sanofi, Takeda/Shire, and UniQure. W.M.: consulting fees from Regeneron Pharmaceuticals, Inc; payment for expert testimony from BioMarin Pharmaceutical, Inc, CSL Behring, and Sobi. G.F.P.: consulting fees from Regeneron Pharmaceuticals, Inc. K.K.: consulting fees from Regeneron Pharmaceuticals, Inc. and Sobi; Director of Research for, and co-owner/founder of, Haemnet Ltd; Honorary Vice President of the UK Haemophilia Society. K.S.: research funding and editorial support fees for the lexicon and associated communications from Regeneron Pharmaceuticals, Inc; consulting fees from Regeneron Pharmaceuticals, Inc. M.P.: research funding and editorial support fees for the lexicon and associated communications from Regeneron Pharmaceuticals, Inc; consulting fees from Regeneron Pharmaceuticals, Inc. M.J.: employee of, and holds stock or stock options for, Regeneron Pharmaceuticals, Inc. A.S.: employee of, and holds stock or stock options for, Regeneron Pharmaceuticals, Inc. L.W.: employee of, and holds stock or stock options for, Regeneron Pharmaceuticals, Inc. V.D.: employee of, and holds stock or stock options for, Regeneron Pharmaceuticals, Inc. M.C.: employee of, and holds stock or stock

options for, Regeneron Pharmaceuticals, Inc. D.E.G.: employee of, and holds stock or stock options for, Regeneron Pharmaceuticals, Inc. I.A.: employee of Intellia Therapeutics, Inc, with compensation and stock options. C.H.: consulting fees for BioMarin Pharmaceutical, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, Regeneron Pharmaceuticals, Inc, Sanofi, and Sobi; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events for BioMarin Pharmaceutical, CSL Behring, LFB, Novo Nordisk, Octapharma Pfizer, Sanofi, Sobi, and Octapharma; support for attending meetings and/or travel from LFB and Sobi; and participation on a Data Safety Monitoring Board or Advisory Board for CSL Behring. S.W.P.: grants to the institution from Siemens and YewSavin, Inc; consulting fees from Apcintex, ASC Therapeutics, Bayer, BioMarin Pharmaceutical, CSL Behring, Freeline, HEMA Biologics, LFB, Metagenomi, Novo Nordisk, Pfizer, Poseida Therapeutics, Regeneron/Intellia, Roche/Genentech, Sanofi, Takeda, Spark Therapeutics, and uniQure; and participation in a scientific advisory board for GeneVentiv Therapeutics and Equilibra Bioscience.

DATA AVAILABILITY

Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing 1) once the product and indication has been approved by major health authorities (e.g., FDA, EMA, PMDA, etc) or development of the product has been discontinued globally for all indications on or after April 2020 and there are no plans for future development 2) if there is legal authority to share the data and 3) there is not a reasonable likelihood of participant re-identification. Submit requests to https://vivli.org/.

REFERENCES

[1] Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020;26:1–158.

[2] Corrigendum. *Haemophilia*. 2021;27:699. https://doi.org/10.1111/hae.14308

[3] Marchesini E, Morfini M, Valentino L. Recent advances in the treatment of hemophilia: a review. *Biologics*. 2021;15:221–35.

[4] Alcedo Andrade PE, Mannucci PM, Kessler CM. Emicizumab: the hemophilia A game-changer. *Haematologica*. 2024;109:1334–47.

[5] Olasupo OO, Noronha N, Lowe MS, Ansel D, Bhatt M, Matino D. Non-clotting factor therapies for preventing bleeds in people with congenital hemophilia A or B. *Cochrane Database Syst Rev*. 2024;2:CD014544. https://doi.org/10.1002/14651858.CD014544.pub2

[6] D'Angiolella LS, Cortesi PA, Rocino A, Coppola A, Hassan HJ, Giampaolo A, et al. The socioeconomic burden of patients affected by hemophilia with inhibitors. *Eur J Haematol*. 2018;101:435–56.

[7] Manco-Johnson MJ, Warren BB. Long-term prophylaxis: what are our options and how to define success? *Hematology Am Soc Hematol Educ Program*. 2022;2022:579–85.

[8] Weyand AC, Pipe SW. New therapies for hemophilia. *Blood*. 2019;133:389–98.

[9] Zhang H, McCarty N. CRISPR-Cas9 technology and its application in haematological disorders. *Br J Haematol*. 2016;175:208–25.

[10] Soroka AB, Feoktistova SG, Mityaeva ON, Volchkov PY. Gene therapy approaches for the treatment of hemophilia B. *Int J Mol Sci*. 2023;24:10766. https://doi.org/10.3390/ijms241310766

[11] De Wolf D, Singh K, Chuah MK, VandenDriessche T. Hemophilia gene therapy: the end of the beginning? *Hum Gene Ther*. 2023;34:782–92.

[12] Vázquez E, Kim M, Santaella ME. Lived experience experts: a name created by us for us. *Expert Rev Hematol*. 2023;16:7–11.

[13] Hermans C, Valentino LA, Thornburg CD, Unzu C, Kay MA, Peyvandi F, et al. A novel gene editing lexicon strategy for the haemophilia community: research plan for development and preliminary results. *Haemophilia*. 2024;30:1272–80.

[14] Centers for Disease Control and Prevention. Diagnosing hemophilia. https://www.cdc.gov/hemophilia/testing/; 2023 [accessed January 29, 2024].

[15] National Bleeding Foundation. Frequently asked questions. https://www.bleeding.org/bleeding-disorders-a-z/treatment/future-therapies/frequently-asked-questions; 2025 [accessed August 30, 2024].

[16] Frangoul H, Altshuler D, Cappellini MD, Chen YS, Domm J, Eustace BK, et al. CRISPR-Cas9 gene editing for sickle cell disease and beta-thalassemia. *N Engl J Med*. 2021;384:252–60.

[17] Gogia P, Tarantino M, Schramm W, Aledort L. New directions to develop therapies for people with hemophilia. *Expert Rev Hematol*. 2023;16:417–33.

[18] Mannucci PM. Hemophilia treatment innovation: 50 years of progress and more to come. *J Thromb Haemost*. 2023;21:403–12.

[19] Leebeek FWG, Miesbach W. Gene therapy for hemophilia: a review on clinical benefit, limitations, and remaining issues. *Blood*. 2021;138:923–31.

[20] Valentino LA, Kaczmarek R, Pierce GF, Noone D, O'Mahony B, Page D, et al. Hemophilia gene therapy: first, do no harm. *J Thromb Haemost*. 2023;21:2354–61.

[21] Hart DP, Branchford BR, Hendry S, Ledniczky R, Sidonio Jr RF, Négrier C, et al. Optimizing language for effective communication of gene therapy concepts with hemophilia patients: a qualitative study. *Orphanet J Rare Dis*. 2021;16:189. https://doi.org/10.1186/s13023-020-01555-w

[22] Miesbach W, O'Mahony B, Key NS, Makris M. How to discuss gene therapy for haemophilia? A patient and physician perspective. *Haemophilia*. 2019;25:545–57.

[23] Astermark J, Blatný J, Königs C, Hermans C, Jiménez-Yuste V, Hart DP. Considerations for shared decision management in previously untreated patients with hemophilia A or B. *Ther Adv Hematol*. 2023;14:20406207231165857. https://doi.org/10.1177/20406207231165857

SUPPLEMENTARY MATERIAL

The online version contains supplementary material available at https://doi.org/10.1016/j.rpth.2025.102710