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Operationalising a haemophilia gene editing lexicon for practical use

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16 Dec 2024 Gene editing lexicon practical use

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Abstract

Introduction: Gene editing therapies offer the possibility of substantial improvement in treatment and quality of life for people with haemophilia (PWH) in a landscape of dynamic therapeutic advancement. Developing a common and understandable language to discuss gene editing will be essential to ensure these treatments can be deployed in a safe and effective manner with fully informed and shared decision-making between healthcare professionals (HCPs) and PWH. A lexicon explaining and clarifying key concepts is one potential tool to address these aims. Here we evaluate how a gene editing lexicon could be deployed to maximise impact and improve patient outcomes.

Aim: To operationalise the gene editing lexicon for successful adoption by the haemophilia community

Methods: Through an innovative, iterative process, representatives from the haemophilia community, including multidisciplinary HCPs, PWH, and caregivers, with support from language strategy experts, developed a gene editing lexicon and evaluated operational aspects for real-world adoption of this resource.

Results: A gene editing lexicon was developed, including infographics illustrating key concepts. Infographics were adapted from the lexicon to further clarify and communicate these concepts. Infographics were found to be a potentially vital tool for enhancing practical use of the lexicon to promote shared decision-making and attain informed consent for gene editing therapies.

Conclusion: A gene editing lexicon shows promise for improving understanding of gene editing for all stakeholders in the haemophilia community. Ensuring the lexicon remains up to date with current therapies and appropriate strategies for adoption such as infographics will enable this resource to have maximum impact.

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1. Introduction

Gene therapies offer the potential of a stepwise improvement in health outcomes for people with haemophilia (PWH).[1] This is because haemophilia offers a promising target for gene therapies to fully restore normal clotting factor levels and improve quality of life. Clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein 9 (Cas9)-based targeted gene editing platforms represent one such emerging treatment option.[2] As a complex novel technology associated with technical vocabulary, it can be challenging to effectively communicate relevant concepts about gene editing. Existing knowledge gaps in gene therapy among patients and other stakeholders adds another layer of complexity. Clear communication of key concepts is crucial for facilitating informed consent and shared decision-making. Given these challenges, a lexicon to promote understanding and communication of gene editing concepts among key stakeholders in the haemophilia community was recently developed.[3,4]

Similar attempts to align key concepts and terminologies have been successfully implemented in many therapeutic areas such as pain control,[5] breast cancer,[6] and Alzheimer's disease.[7] Lexicons that are accurate, consistent, and intelligible have also been developed to promote effective communication of gene therapy concepts in haemophilia and address identified knowledge gaps.[8] Glossaries relating to haemophilia gene therapy for use as patient communication aids have also been developed.[9] To date, the recently developed lexicon is the only such resource specifically focused on gene editing. Unlike previously available lexicons, the gene editing lexicon is also unique in that it was developed using an innovative approach involving close partnerships among major stakeholders in the patient haemophilia community (including patient organisations and caregivers), scientific organizations, and biotechnology organisations. There is a need to address how best to utilise existing resources to ensure equitable and uniform access to gene editing therapies.

Several challenges exist regarding operationalisation of the gene editing lexicon. An urgent need to design communication and information campaigns on new therapeutics such as

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gene therapy for clinical staff and patients has previously been highlighted.[10] Many healthcare professionals (HCPs) and patients only have a basic understanding of gene therapy.[11] Previous surveys have found that 40% of haematologists specialising in haemophilia consider their ability to discuss gene therapies with patients to be “limited”.[12] Data have shown that there is a need for new strategies for provider education to increase confidence in discussing gene therapy.[13] Here, we report our findings on strategies successful adoption of the gene editing lexicon by all the stakeholders in the haemophilia community with the potential to lead to improvements in patient care.

2. Materials and Methods

2.1. Study design and setting

The study design for the lexicon development has been described previously.[4] Briefly, through an innovative, iterative process, representatives from the haemophilia community, including multidisciplinary HCPs, PWH, caregivers, individuals associated with professional organisations, and patient advocacy groups, with support from language strategy experts, developed a gene editing language lexicon. To ensure that lexicon contents are accessible to audience with wide background, general principles of gene editing were described first before delving into more advanced topics on gene insertion including introducing it as a type of gene editing. The final lexicon was developed in English language and portions of it will be translated to other languages as needed with support from language experts. The entire process was overseen by the lexicon steering committee at each stage (Figure 1). This work was conducted between August 2023 and May 2024 and utilised a seven-stage cumulative approach.

2.2. Development of lexicon infographics

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During the lexicon development process, it was indicated that visual, educational aids, including infographics, would be important adjuncts to deploy lexicon language in real-world settings such as clinics and within patient organisations. Therefore, infographics targeted at HCPs and lived experience experts (LEEs; patients, their families, and their caregivers) that visualised lexicon language were developed by the lexicon steering committee. The initial draft of the infographics was consulted with a panel of patient experts from the National Bleeding Disorders Foundation (NBDF) in a virtual advisory board, with support from language strategists. Infographics were eventually reviewed and optimised by the lexicon steering committee before finalising.

2.3. Operationalisation survey

Global experts in the field of bleeding disorders, including representatives from academic institutions, healthcare providers, scientific organizations, and patient organizations (N=11; Figure 2) were consulted via an electronic survey to explore real-world barriers and enablers for operationalising the gene editing lexicon and were asked to answer six relevant questions (Table 1). Qualitative data were manually coded and analysed by thematic analysis to understand how the gene editing lexicon could be operationalised for practical use to improve communication regarding gene editing and patient outcomes.

3. Results

3.1. Development of lexicon infographics

Feedback obtained during lexicon development indicated that visual aids should be considered a crucial part of operationalisation strategies. Development of practical approaches to using the lexicon was deemed essential for uniform access and adoption. Therefore, infographics were highlighted as potentially valuable aids for deploying the gene editing lexicon. Infographics were developed with critical input from patient experts at the

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NBDF, and were reviewed and optimised by the lexicon steering committee prior to finalising. One of the figures from the infographics describing gene insertion is shown in Figure 3 for illustrative purposes. A detailed, four-page set of infographics visualising lexicon language is available upon request from the authors.

The infographics present lexicon language in the frequently asked question format. For concepts considered to be especially critical (for example, the *in vivo* nature of therapy), information was included more than once. Analogies from the gene editing lexicon and use of “deeper dive” sections (which give additional information) were used to clarify more complex information. Throughout the document, colour choices were selected to be consistent and maximise visual effect. For instance, factor IX gene graphics were coloured in purple, whereas all other information relating to CRISPR technology was coloured in orange.

3.2. Expert consensus on operationalising a gene editing lexicon

Several key themes emerged from the electronic survey of global experts on the potential real-world impact of the gene editing lexicon in clinical, academic, and patient organisation settings (Table 1). Respondents agreed that the gene editing lexicon could be used to educate both providers as well as service users, helping to distinguish between gene editing and other gene therapy approaches. Respondents also reported that having this tool freely available would save time and costs for healthcare and patient organisations that are developing educational materials. Most respondents said that they would share this resource with colleagues and patient organisations.

The survey identified several potential barriers to the adoption of a gene editing lexicon. For instance, there was concern that a gene editing lexicon could only have significant impact if promoted effectively, making it clear that its use is free of copyright and that it can be reproduced and distributed. In addition, different institutional approaches to adopting and disseminating the lexicon were identified as a possible barrier. Other highlighted barriers to adoption of the lexicon were resource limitations (including time and funding for educational

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activities). Attitudes within the bleeding disorder community were also raised as a potential barrier to dissemination of the lexicon, including failure to recognise the value of new treatments and hesitancy towards seeking out alternative therapies.

The survey also generated potential solutions to some of the perceived barriers to adoption of the gene editing lexicon. These included ensuring there was an effective promotion campaign to raise awareness of the gene editing lexicon and ensuring institutions adopt policies that protect educational time to acquire knowledge about gene editing therapies and other best practice updates. Respondents also stated that HCPs and organisations should seek to identify resources to facilitate and support educational events for HCPs and LEEs.

Respondents showed enthusiasm towards development of multimedia and visual aids to operationalise the lexicon, especially in the family and paediatric settings. One respondent felt that LEEs are often “visual learners” and that infographics present information in a way that is “accessible”. Respondents stated that infographics would be very useful for including in pamphlets and “take-away” resources. One respondent proposed that infographics could form the basis of other educational resources such as short videos or podcasts.

Overall, respondents were very positive about the prospect of using a gene editing lexicon to promote shared decision-making and informed consent. It was felt that lexicon language could form the basis of shared consent documents and that in particular, infographics would be useful to demonstrate vital concepts. The process of developing a lexicon as a co-creation between LEEs and HCPs was felt to be of particular significance for enhancing the ability of the lexicon to fully inform and ensure terminology remains clear and consistent.

4. Discussion

4.1. Use of infographics to operationalise the gene editing lexicon

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Health literacy is the ability of LEEs to find, understand, and use information and services that are relevant for their medical condition.[14] In the haemophilia community, poor health literacy has been shown to impact adherence to treatment and lead to sub-optimal health outcomes.[15] The US Department of Health and Human Services' "Healthy People" programme outlines that the responsibility to make health-related information more equitable and comprehensible lies upon organisations, including HCPs.[14] Development of the gene editing lexicon and infographics to target LEEs and healthcare organisations represents one such solution.

Infographics and visual aids, including multimedia resources, are effective tools for communicating health information.[16] Overtly technical language might inhibit patient participation in treatment decisions, leading to poorer health outcomes and non-adherence.[17] The infographics that were developed based on the gene editing lexicon emphasise plainspoken over technical language, with the goal of equipping LEEs with the knowledge required to fully participate in making shared healthcare decisions and promoting informed consent. Infographics have been shown to be an effective tool to support patient-centric and shared decision-making between LEEs and HCPs regarding gene therapy.[18] HCPs could use such resources as visual aids during patient consultations when discussing gene editing.[19] Therefore, we propose that these infographics would be useful in the setting of clinical trials and future prescription of licensed gene editing therapies.

Gene therapies, rather than being an index event for LEEs, should be considered in terms of a patient journey that may extend throughout the life span.[18] A gene editing infographic could have particular application at the pre-gene therapy information-seeking and decision-making stages, clarifying key processes and basic scientific concepts. Our infographic augments language, such as the analogy of the vector as a "package", which has been validated and suggested by other groups.[9] Given the emphasis on personalising care and engaging LEEs in treatment decisions,[20] infographics have the potential to facilitate decision making, enabling timely treatment and complying with treatment regimens.

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4.2. Other aspects of operationalising the gene editing lexicon

Our survey of global experts on operationalising the gene editing lexicon emphasised that it could form the basis for developing new educational materials that have the potential to be cost saving. Developing patient educational materials can represent a significant expense for healthcare organisations, with the average cost of developing one educational pamphlet having been estimated at up to $7000.[21] A freely available gene editing lexicon made accessible to the bleeding disorder community could save HCPs and patient organisations significant expense. Accordingly, the lexicon and pertaining educational tools based upon this lexicon are planned to be disseminated via patient organisations such as WFH and EHC as well as HCP organisations such as the American Society of Hematology, the International Society on Thrombosis and Haemostatis, and the European Association for Haemophilia and Allied Disorders.

Experts also suggested that the gene editing lexicon represented a resource that could be shared among colleagues. Knowledge sharing is known to be necessary for adapting, extending, and creating new knowledge and innovation.[22] Conversely, failure to share medical knowledge is known to adversely affect patient safety.[23] Therefore, the gene editing lexicon and associated infographics have the potential to improve patient safety. Potential ways of sharing learning from the lexicon between HCPs include face-to-face settings, such as conversation in clinical settings and seminars, and virtual settings, such as online educational events, email, and social media.

Experts felt that the gene editing lexicon could be utilised to improve shared decision-making. Shared decision-making, whereby LEEs and clinicians collaborate to make healthcare decisions based on clinical evidence and patient priorities, is an established and aspirational concept.[24] An urgent need to develop tools to facilitate shared decision-making regarding new therapies has recently been recognised.[13] Hermans et al. state that patient education is critical to shared decision-making, in particular ensuring that LEEs'

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understanding is improved using jargon-free terminology.[25] They also highlighted the need to educate all members of the patient-facing multidisciplinary team, including nurses, physiotherapists, and psychologists. Therefore, it is envisioned that gene editing lexicon can inform future iterations of shared decision-making documents such as the WFH tool. Additionally, this lexicon could be deployed to promote key aspects of learning when developing patient and HCP educational programmes, as part of the effort to improve shared decision-making processes.

Associated with the ambition to improve shared decision-making processes, we propose that the gene editing lexicon could be operationalised to optimise informed consent processes for patients considering a gene editing therapy. A need for more creative communication of information, including use of media (for example, infographics), in the informed consent process for gene therapies has been described.[26] Multimedia tools can help optimise the consent process by personalising the experience, synthesising content, and minimising "information overload", allowing information to be presented in more user-friendly ways.[27,28] Therefore, as a next step for operationalising the gene editing lexicon, an educational video summarizing its key aspects has also been developed (available upon request from authors).

It should be acknowledged that while this lexicon is being deployed, there are still many unanswered questions about gene editing therapies, including long-term efficacy and safety. This lexicon will require adaptation and modification as improvements emerge in the understanding of CRISPR-based and other types of gene editing across the haemophilia community. As this knowledge is obtained, there is potential to update the lexicon to ensure its continued impact and utility.

5. Conclusion

There is an urgent need to promote education about novel therapies in the bleeding disorder community, including gene editing therapies. A lexicon developed through collaboration

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between key stakeholders in the haemophilia community shows promise as a potential vehicle to improve understanding of gene editing therapies. Therefore, it is well positioned to have a functional and meaningful impact on this community through the development of educational materials, informed consent forms, and shared decision-making tools. Future efforts will focus on assessing improvements in understanding of CRISPR-based and other types of gene editing across the haemophilia community, with the goal of further improving the positive impact of this lexicon on patient care.

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Author Contributions

William McKeown and Micheala Jones were involved in conceptualization of the manuscript. All authors interpreted the data, contributed to critically revising the manuscript and approved the final draft.

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Conflict of Interest Statement

WMc reports consulting fees from SOBI, Pfizer and CSL-Behring. . **CH** has received research funding from Bayer, CSL Behring, Novo Nordisk, Pfizer, Shire/Takeda, and Sobi; honoraria and speaker's bureau from Bayer, CAF-DCF, CSL Behring, Hoffmann-La Roche, LFB, Novo Nordisk, Octapharma, Pfizer, Shire/Takeda, Sobi, BioMarin Pharmaceutical, Regeneron Pharmaceuticals Inc., and UniQure. **CU** has grant funding from Pfizer. **MAK** is inventor of a filed patent held by Stanford University; and cofounder, serves on the board of directors and scientific advisory board, and is a consultant for LogicBio Therapeutics. **FP** reports consulting fees from BioMarin Pharmaceutical, CSL Behring, Grifols, Roche, Sanofi, and Sobi; and honoraria from Spark Therapeutics and Takeda. **PS** is a steering committee member for Regeneron Pharmaceuticals, Inc. **WM** reports research/grant funding, speaker fees/travel support or participation on an advisory board for Bayer, Biomarin, Biotest, CSL Behring, Chugai, Freeline, LFB, Novo Nordisk, Octapharma, Pfizer, Regeneron Pharmaceuticals, Inc., Roche, Sanofi, Sobi, Takeda/Shire, and UniQure. **GFP** reports

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membership of the board of directors of the World Federation of Hemophilia and Voyager Therapeutics, and scientific advisory board for Be Bio; and consultancy for BioMarin Pharmaceutical, Decibel, Frontera, Metagenomi, and Regeneron Pharmaceuticals, Inc. **KK** has received research/grant funding or speaker fees from Biomarin, CSL Behring, Hemab, Novo Nordisk, Pfizer, Roche, Sobi, and Spark. **LAV** is former president and chief executive officer of the National Bleeding Disorders Foundation (NBDF). **SWP** reports consultancy for Apcintex, ASC Therapeutic, Bayer, BioMarin Pharmaceutical, CSL Behring, HEMA Biologics, LFB, Novo Nordisk, Pfizer, Precision Biosciences, Roche/Genentech, Sanofi, Spark Therapeutics, Takeda and UniQure; and grants/research funding from BioMarin Pharmaceutical, Freeline, Genentech/Roche, Sanofi, and UniQure. **MP** reports consultancy fees from Regeneron Pharmaceuticals, Inc; **MJ, VD, AS** and **DEG** hold stock or stock options for, and are employees of, Regeneron Pharmaceuticals, Inc. **CMK** reports grants/research support from Bayer, Genentech, Octapharma, and Regeneron Pharmaceuticals, Inc.; consultancy fees/honoraria from Bayer, Biogen, BioMarin Pharmaceutical, CSL, Genentech, Novo Nordisk, Octapharma, Pfizer, and Takeda; and participation in a data and safety monitoring board for Bayer and Octapharma.

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Data Availability Statement

Qualified researchers may request access to study documents (including the lexicon development framework and operationalisation survey) that support the methods and findings reported in this manuscript. Individual anonymised 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

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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/

Ethics Statement

The methodology was approved by the lexicon steering committee. All participants provided written informed consent before participating. The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines.

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Table 1. Electronic survey questions on operationalising the gene editing lexicon

1)	What organisations in the bleeding disorder community are you affiliated with?
2)	How would you use a lexicon to benefit the work of your organisation? (list all possibilities)
3)	What barriers exist to use of a lexicon in the work of your organisation?
4)	What steps or additional resources would allow you to overcome these barriers?
5)	How would multimedia and educational/visual aids enable you to use the lexicon?
6)	How would you utilise the lexicon to develop consent forms and shared decision-making tools?

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FIGURE 1.

Seven-stage approach to development of the gene editing lexicon with oversight by the lexicon steering committee

FIGURE 2.

Responses to the electronic survey questions on operationalising the gene editing lexicon

FIGURE 3.

Infographic explaining gene editing and the application of CRISPR-based targeted gene insertion for the treatment of haemophilia

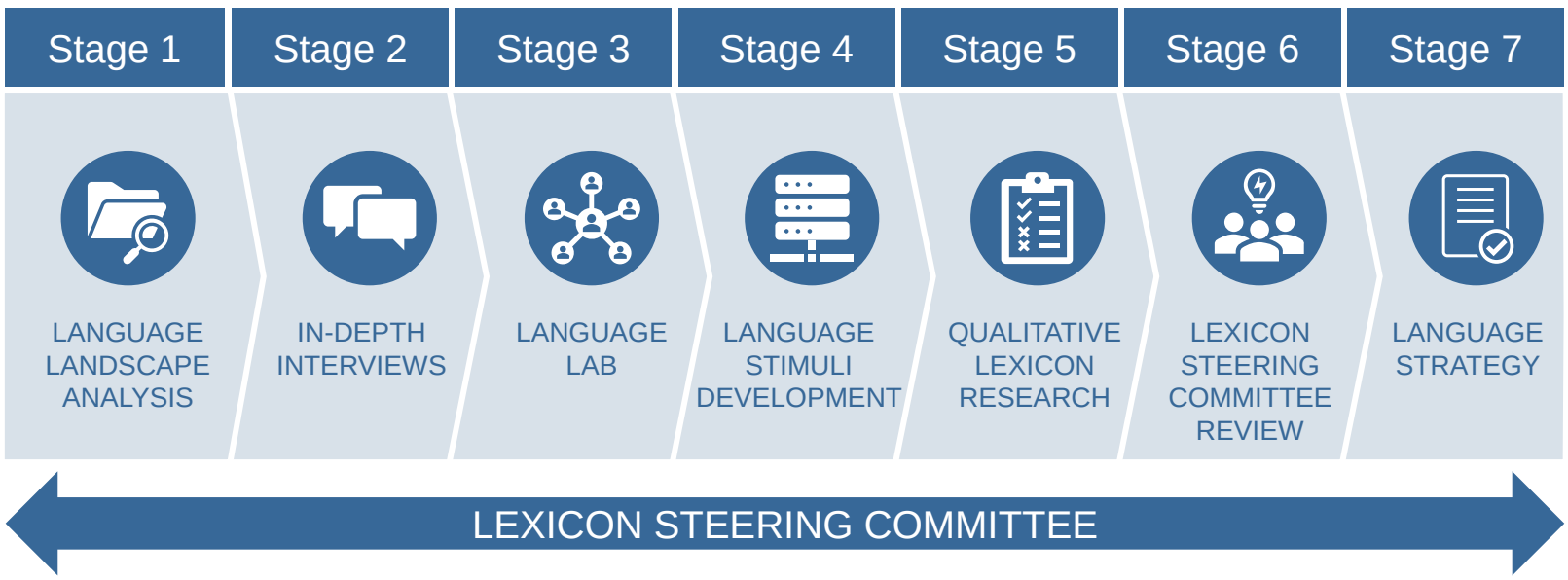
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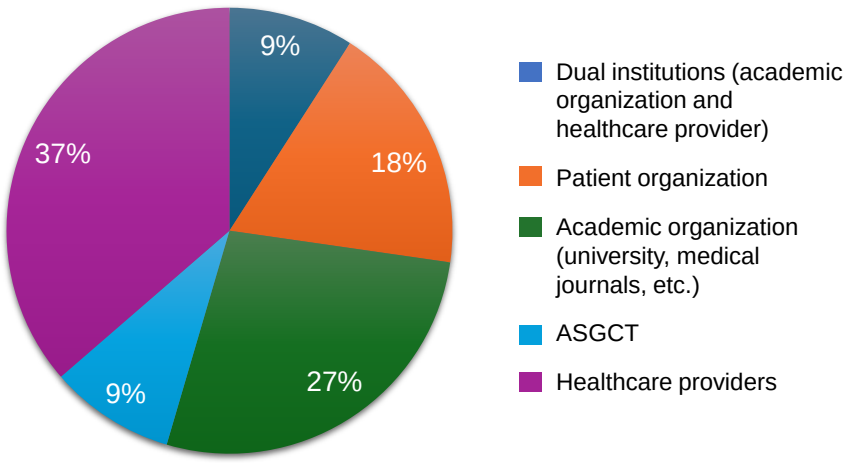
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Figure 1



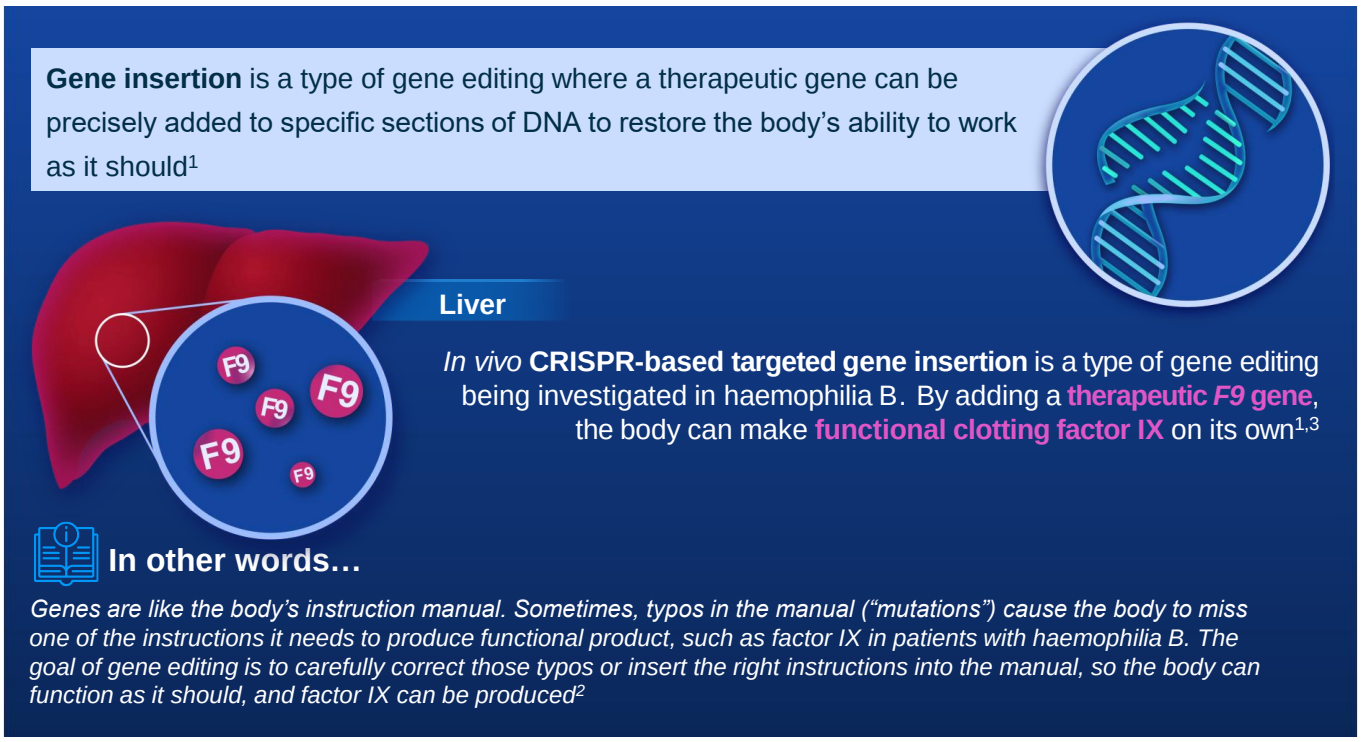
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Figure 2



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Figure 3



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