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RESEARCH ARTICLE

REVISED Public perceptions and willingness to accept somatic gene therapy: A Belgian survey study

[version 4; peer review: 4 approved, 1 approved with reservations]

Previously titled: "Public perception and willingness to accept somatic gene therapy: A Belgian survey study"

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Abstract

Background

Genetic disorders affect millions worldwide, yet fewer than 10% of patients currently receive effective treatment. While gene therapies offer significant promise, their clinical translation is hindered by technical, regulatory, and societal challenges. Low enrolment rates in clinical trials, ethical concerns surrounding inclusion criteria, and uncertainty about preventive applications all contribute to slow progress. Public perception plays a crucial role in shaping trial participation and the integration of gene therapies into healthcare systems. This study examines public attitudes in Belgium to support the responsible development and implementation of gene therapy trials.

Methodology

A cross-sectional online survey using convenience sampling was conducted in Belgium with adults (18+) recruited through local

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pharmacies. The survey included 12 items assessing self-reported knowledge of gene therapy and willingness to accept gene therapy. To evaluate willingness to accept, hypothetical vignettes were used, which varied by treatment characteristics (e.g., side effects, efficacy, limited evidence), patient age (5, 20, 65 years), and symptomatic status (symptomatic, asymptomatic with uncertain or expected future symptoms). Descriptive statistics summarised all items included in the questionnaire.

Results

The sample included 289 participants, of whom 67% had completed higher education, 64% had children, and 87% had heard of gene therapy before. Overall willingness was high. Attitudes were generally positive, with limited concerns about its experimental features (e.g., unknown side effects (12%), long-term effects (8%), and uncertain effectiveness (8%)). However, key barriers included fears of altered identity (39%), external pressure (38%), and skepticism about its novelty (31%). Uncertainty about symptom development consistently reduced willingness. Patients' age played a secondary role, with younger individuals generally receiving higher support for gene therapy than older adults.

Conclusion

Public attitudes toward gene therapy were largely positive, guided by perceived benefits over scientific certainty. Support favored curative over preventive use, with participants balancing autonomy and medical guidance in shared decision-making.

Keywords
Gene therapy, public acceptance, curative therapies, ethics

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REVISED **Amendments from Version 3**

The revised manuscript integrates the reviewers' feedback and includes additional clarification on survey questions' wording and clarity, along with an expanded discussion of study limitations related to the informational video, survey elements, and translation of materials provided in the supplementary files.

Any further responses from the reviewers can be found at the end of the article

Introduction

Genetic disorders affect millions of people worldwide, yet effective treatments are available for only a small subset of patients.[1] Advances in gene editing technologies, such as CRISPR-Cas9, enable precise genome modifications,[2] making somatic gene therapy (a treatment targeting non-reproductive cells) a promising approach for inherited and acquired diseases. Although the initial introduction of gene therapies during the early 1990s was met with considerable optimism, this enthusiasm was tempered by a series of disappointing clinical trials outcomes. Many early experimental therapies failed to demonstrate clinical benefits or resulted in unexpected toxicities, some of which led to widely publicized patient deaths.[3] Progress over the past decade in safety, delivery, and gene transfer has enabled regulatory approval of several therapies.[3]

Despite its therapeutic potential, translating somatic gene therapy into clinical practice still faces several challenges. Because many gene therapies target very small, rare disease populations, and because these patients often experience significant delays in obtaining an accurate diagnosis while facing life-threatening conditions, clinical trial recruitment is inherently limited. Beyond these structural constraints, low participation in clinical trials remains persistent, as many eligible individuals hesitate due to unknown long-term effects, adverse side effects, and the therapy's experimental status.[4] At the same time, researchers face complex ethical and methodological challenges in defining inclusion and exclusion criteria. Determining whether to enrol children, older adults, or patients at different disease stages involves ethically sensitive and context-specific considerations. For instance, recent work on gene therapy trials for sickle cell disease highlights tensions between strictly defined eligibility rules and the need for informed, shared decision-making that accounts for patient preferences rather than rigid criteria alone, illustrating how trial design decisions may unintentionally restrict access for patients who might benefit from participation (https://ashpublications.org/bloodadvances/article/10/3/608/547809/Informed-shared-decision-making-or-rigid). These decisions can have far-reaching consequences, influencing both the success and generalizability of clinical trials, as well as public trust in the research process.[5]

Patients with progressive genetic conditions stand to benefit significantly from gene therapy designed to halt or slow down disease progression. Administering such therapies at an early stage could not only prevent severe, potentially life-threatening complications, but also serve as a preventive intervention to limit further damage.[6] Although gene therapy is most often presented as a cure, this framing remains debated given limited long-term follow-up data. Nevertheless its effects are currently considered potentially durable.[7] Public support tends to be stronger for treating severe or life-threatening conditions. In contrast, greater ambivalence exist regarding treatment of asymptomatic individuals genetically predisposed to disease later in life, and attitudes towards its preventive use remain unclear.[8]

Over the years, numerous studies have explored public attitudes toward gene therapy, with a particular focus on perspectives concerning germline-editing, human enhancement and disease-specific applications. A systematic review (2020) examining the publics acceptability of gene therapy and gene editing found the highest support for applications addressing serious conditions without alternative treatments. However, this support was often tempered by concerns about the long-term safety, potential unknown side effects, and broader ethical implications of genetic modification.[9] Studies in countries such as Germany, France, and Italy reveal a similarly complex picture, with participants expressing both optimism and caution, often noting concerns about the novelty of the technology and its potential for misuse.[10]

These findings suggest that public perception toward gene therapy and related technologies depends on context. Surveys and public engagement initiatives have demonstrated the importance of integrating societal perspectives early in the research and development process. Such initiatives not only improve transparency and foster public trust but also help to identify potential sources of resistance or misunderstanding that could hinder clinical progress. Moreover, they also allow for a more inclusive approach to science and innovation, in which societal values and ethical considerations are integrated into research design and governance structures.[8,11,12] The success of early-phase clinical trials, participant recruitment efforts, and eventual incorporation into healthcare systems heavily depend on how these therapies are perceived and understood by the general public.[13]

In Belgium, public attitudes toward somatic gene therapy remain relatively underexplored. Given the country's active involvement in biomedical research and its central position in EU-level regulatory processes, it is essential to investigate how the public understands and evaluates these emerging technologies.

This study aims to address this gap and support clinical trial design, policy, and public communication for socially responsive governance of gene therapy in Belgium and Europe.

Methods

This study involved a cross-sectional online survey conducted using convenience sampling among individuals living in Flanders.

Questionnaire development

The questionnaire assessed participants' willingness to accept gene therapy; attitudes toward somatic gene therapy, focusing on the conditions under which participants would consider its use and the factors influencing its acceptability (data file 1).[14] The 12-item questionnaire covered the following subcategories: i. Socio-demographic information, ii. Self-reported knowledge of gene therapy, followed by a brief informational video introducing gene therapy, iii. Willingness to accept gene therapy across various hypothetical vignettes, and iv. Attitudes towards the ethical considerations. The informational video (2m17s, data file 2)[14] supported sections three and four of the questionnaire and was based on information from ErfoCentrum, an organisation providing reliable and independent health information.[15] More specifically, the animated video provided information on the nature of genetic conditions and how gene therapy can be used to treat such conditions. It also explained how gene therapy targets the genetic mutation, the use of (viral) vectors and the therapeutic aim of the treatment.

To evaluate willingness to accept gene therapy, section three of the questionnaire presented a series of hypothetical vignettes that varied by treatment characteristics (e.g., side effects, efficacy, limited evidence), patient age (5, 20, 65 years), and symptomatic status (symptomatic, asymptomatic with uncertain or expected future symptoms). The chosen age groups were based on the case design of Ormondroyd et al. (2024),[16] who used ages 5, 20, and 50 years, with 50 being replaced by 65 years to better capture differences in life stage, responsibilities, and social context. Participants indicated in which scenarios they would be willing to accept gene therapy as a treatment option. Vignette design and key variables were informed by previous research on patient preferences and public attitudes.[12,16–18]

The fourth section of the questionnaire included the assessment of 12 ethical considerations related to gene therapy (e.g., perceived changes in identity, conflicts with moral beliefs and/or nature), as identified by previous research on public attitudes toward gene therapy.[8,12] Participants indicated how each factor affected their acceptance using a five-point Likert scale.

A pilot study, involving six Dutch-speaking individuals, evaluated the clarity and comprehensibility of the questionnaire and the informational video. No further adjustments were needed.

The anonymous questionnaire was available in Dutch and administrated either in paper format or through an online platform (Lime Survey Version 6.10.0).[19]

Participant recruitment

Eligibility criteria required participants to be Dutch-speaking adults (18+) who resided in Belgium. A convenience sample was recruited through three public pharmacies in Flanders. Participants were personally invited and could complete the survey on paper, using a tablet, or by scanning a QR-code on a flyer. Data collection took place in December 2024.

Data analysis

The dataset (data file 3)[14] was cleaned prior to data analysis, with responses excluded based on the following criteria: i) questionnaires completed only up to section two, ii) duplicate open-ended responses combined with identical demographic characteristics, and iii) suspected straight lining. To identify potential straight lining, the most frequently selected response option was determined for each group of questions. If this option accounted for more than 85% of responses across all sub-items, the pattern was flagged as a possible indication of straight lining. As the questionnaire included three sections, responses were excluded if more than one-third of these sections met the criteria for suspected straight lining.

Subsequent descriptive statistics were performed using SPSS Statistics software (29.0.2.), to generate frequency distributions.

Ethics
The study obtained ethical approval from the Ethics Committee Research UZ/KU Leuven (MP032851). The survey was anonymous, and therefore informed consent was not required.

Results
A. Socio-demographic characteristics
Of the 375 individuals who accessed the questionnaire, 86 responses were excluded from the dataset during the data cleaning process. The final sample consists of 289 individuals (94 men and 195 women) with a mean age of 47 years (SD = 17.1; 95%CI: 44.8–48.7) (Table 1). Most respondents had attained higher education (67.1%), had children (63.7%) and identified as Catholic (54.0%). Among those who reported a religious affiliation (n = 163), 80% indicated that their religion was either not important (43.6%) or only slightly important (36.8%) in guiding their daily decision-making.

Before watching the video, most respondents reported having heard of gene therapy (86.5%), but most were unable to explain it (64.7%). After viewing the video, respondents reported feeling rather (56.1%) or very (21.1%) capable of making an informed decision about receiving gene therapy.

B. Willingness to accept gene therapy
1. Treatment characteristics

Overall, respondents demonstrated a general willingness to accept gene therapy as a treatment across the various vignettes (Table 2). A substantial proportion reported a willingness to proceed with gene therapy despite uncertainties, including unknown long-term effects (76.1%), uncertain effectiveness (70.9%) and the possibility of unknown side effects (60.6%). Moreover, almost half of the respondents stated that they would not delay initiating gene therapy either until (i.) their condition progresses to a more severe stage (50.5%), or (ii.) until greater clarity regarding these uncertainties became available (47.5%). The majority expressed high trust in their doctor, with 86.2% relying on their recommendation before starting treatment.

Table 1. Socio-demographic characteristics of study participants (n = 289).

		N	Valid %
Sex	*Male*	94	32,5
	Female	195	67,5
Education	*No diploma*	8	2,8
	Secondary education	81	28,0
	Higher education	194	67,1
	Other (e.g., Ph.D., postgraduate, etc.)	6	2,1
Children	*Yes*	184	63,7
	No	105	36,3
Religion	*Protestants*	4	1,4
	Catholic	156	54,0
	Muslim	3	1,0
	None	120	41,5
	Other	6	2,1
Importance religion (n = 163)	*Not important*	71	43,6
	Slightly important	60	36,8
	Rather important	20	12,3
	Very important	8	4,9
	Super important	4	2,5

Table 2. **Gene therapy acceptance in relation to treatment characteristics (n = 289).**

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
I would agree to gene therapy despite the **unknown long-term** effects.	0,7	6,9	16,3	57,1	19
I would agree to gene therapy despite the risk of possible **unknown side effects** in the future.	0,3	12,1	27	47,8	12,8
I would agree to gene therapy despite current uncertainty about its **effectiveness** and **duration** of effects.	0,0	7,6	21,5	56,4	14,5
I prefer to wait with starting a new therapy until my **illness becomes more severe**.	10,4	40,1	21,1	24,6	3,8
I prefer to wait for **more clarity** about safety, effect, and consequences, even if that means risking worse symptoms later.	7,6	39,8	29,1	21,5	2,1
If I decide to start the treatment, I trust my **doctor's advice**.	0,3	1,7	11,8	56,1	30,1

Shading in the tables is used to visualize regions with the greatest participant density (percentage of participants). Results related to the following case: "Suppose you have a genetic disease. The symptoms of your illness strongly affect your daily life. You experience difficulties performing household tasks, have problems with mobility, face limitations in social activities, and you are unable to sustain a full workday. Your condition also worsens with age, increasingly impacting your life. There is now a new gene therapy available which, as the only treatment, can stop the progression of your disease. However, because this therapy is new, scientists still know little about its effectiveness, long-term effects, and possible side effects."

Table 3. **Gene therapy acceptance for different patient profiles (n = 289).**

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
You are the parent of a **5-year**-old child with a genetic disease, but the child currently has **no symptoms.** Doctors expect future issues.	5,3	33,3	33,3	23,5	4,6
You are the parent of a **5-year**-old child with a genetic disease who currently has **no symptoms**. It is **uncertain** whether symptoms will develop.	22,8	42,5	27,0	7,4	0,4
You are the parent of a **5-year**-old child with a genetic disease who currently **experiences symptoms** that strongly affect daily life.	0,4	2,5	14,7	60,7	21,8
You are **20 years** old and have a genetic disease, but currently experience **no symptoms**. Doctors **expect** future issues.	4,9	30,2	26,0	34,4	4,6
You are **20 years** old and have a genetic disease, but currently experience **no symptoms**. It is **uncertain** whether symptoms will develop.	16,5	43,5	28,4	10,2	1,4
You are **20 years** old and have a genetic disease that **currently causes symptoms** strongly affecting your daily life. These will worsen over time.	0,0	2,1	7,0	57,9	33,0
You are **65 years** old and have a genetic disease, but are currently experiencing **no symptoms**. Doctors expect future issues.	6,7	35,4	27,0	24,6	6,3
You are **65 years** old and have a genetic disease, but currently experience **no symptoms**. It is **uncertain** whether symptoms will develop.	19,3	42,5	25,6	9,5	3,2
You are **65 years** old and have a genetic disease that currently **causes symptoms** that strongly affect your daily life.	1,1	2,8	11,6	56,1	28,4

Shading in the tables is used to visualize regions with the greatest participant density (percentage of participants). Results related to the following question: "In the following statements, indicate the extent to which you agree with the consideration to undergo gene therapy, taking into account the age and stage of the disease."

2. Patient profiles

Table 3 shows that uncertainty about symptom development consistently decreased willingness across all patient profiles, while treatment was more strongly favored for younger adults. More specifically, in pediatric scenarios, opinions on treating asymptomatic children were divided, with 28.1% expressing support and 38.6% opposing treatment. Support dropped significantly to just 7.8% when symptom development was uncertain. However, when the child was symptomatic and their daily life was affected, support for gene therapy rose sharply to 82.5%.

Similar trends were observed across other age groups. For a 20-year-old adult with expected symptom onset, 39% supported gene therapy, while 35.1% were opposed. Support declined to 11.6% when symptom onset was uncertain, but increased substantially to 90.9% when the individual was symptomatic and their condition was worsening.

Among 65-year-olds, support was lower overall; 30.9% were in favour of treatment in asymptomatic cases with expected symptom onset, and only 12.7% supported it when symptom progression was uncertain. Conversely, 84.5% supported therapy when symptoms were present.

3. Ethical considerations

Information-related factors had the strongest positive influence; 92.2% indicated that receiving sufficient information would positively impact their decision, and 89.4% reported that fully understanding the therapy would have a similar effect (Table 4). Perceptions of novelty and risk were approached with caution. The fact that few individuals had previously received gene therapy was viewed negatively by 30.7%, whereas the use of viruses raised similar mixed reactions (56.9% neutral), reflecting widespread uncertainty regarding technical aspects.

External pressure from doctors or family members was mostly perceived negatively, with 38.2% of respondents rating it as a negative influence. Moral or religious objections appeared to have less impact, as nearly half (48.4%) indicated these would not affect their decision. In contrast, views were more divided regarding concerns about potential changes to identity and personality, with 39.3% perceiving this negatively. Reproductive considerations elicited similarly mixed responses, though most participants indicated they would not let it influence their decision (44.2%).

Table 4. Gene therapy acceptance in relation to ethical considerations (n = 289).

	Very negative	Negative	Neutral	Positive	Very positive
Receiving **sufficient information** about the therapy	0,4	1,1	6,4	60,4	31,8
Fully understanding what gene therapy involves	0,0	0,4	10,2	52,7	36,7
Possible future changes in my identity/ personality	7,1	32,2	37,5	15,9	7,4
Passing on **genetic changes** to my children	7,8	18,7	29,3	27,9	16,3
The idea that gene therapy goes **against nature**	6,4	16,6	58,7	12,4	6
Pressure from doctors or family members to make a decision	7,8	30,4	39,9	20,5	1,4
The idea that gene therapy goes against my **moral or religious beliefs**	14,1	18	48,4	12,7	6,7
Use of a **virus** in the therapy	2,8	12,4	56,9	21,2	6,7
Availability of the therapy in my area	1,8	5,3	41,7	42,4	8,8
The fact that few people have **received** gene therapy before me	3,5	27,2	44,5	18,4	6,4
Affordability of the therapy for **society** (actual cost of gene therapy)	2,5	12	50,9	28,3	6,4
Affordability of the therapy for **yourself** (personal cost contribution to gene therapy)	1,8	21,2	35	34,3	7,8

Shading in the tables is used to visualize regions with the greatest participant density (percentage of participants). Results related to the following case: "Suppose you had to decide tomorrow whether to undergo gene therapy. To what extent would the following aspects influence your decision to take or not take the therapy? Here, "negative" means it would lead you to decide not to undergo the therapy, and "positive" means it would lead you to decide to undergo the therapy. "Neutral" means it would have no influence on your choice."

Conversely, economic and practical factors were more positively perceived. The affordability of the treatment to the patient was viewed as a positive factor by 42.1% of participants, and societal affordability by 34.7%. The local availability of the therapy was rated positively by a majority (51.2%).

Discussion

To our knowledge, this survey is the first to explore how the public in Flanders perceives gene therapy. While gene therapy is not new, it remains unfamiliar to most participants. Overall, participants expressed generally positive attitudes despite its experimental aspects. Yet, ethical ambivalence persists around identity, heritability, and external influence, while perceptions of novelty and risk were cautiously neutral. In contrast, clear information and understanding significantly enhanced acceptance.

The experience of symptoms emerged as the most influential factor shaping support. Uncertainty about symptom development consistently reduced willingness across age groups. Whereas, age played a secondary role, with younger individuals receiving higher support than older adults in comparable situations.

Acceptance shaped by trust and justice

Our study participants were open to the idea of gene therapy, despite acknowledging uncertainties around long-term safety and efficacy. This openness may reflect a kind of pragmatic reasoning: when faced with serious or progressive conditions, individuals often show a greater willingness to accept scientific uncertainty. As Jasanoff *et al.* (2018) argue, public support for gene editing is frequently shaped more by therapeutic intent and perceived benefit than by a demand for complete scientific certainty.[20] Interestingly, participants were relatively unfazed by the technical novelty of gene therapy. The use of viral vectors or the limited number of prior patients did not significantly deter them, but these factors were not strong motivators either. This cautious ambivalence echoes previous studies, which have found that the public tends to adopt a "wait and see" attitude toward new biomedical technologies.[21]

When it came to potential risks to identity or future generations, the responses were more mixed. Some participants expressed concern about changes to identity or unintended heritable effects, while others were more neutral. This ambivalence reflects long-standing ethical debates around what it means to "intervene" at the genetic level, especially in ways that could affect one's sense of self or future offspring.[20]

Finally, while identity and heritability raised theoretical concerns, it was more practical issues like affordability and availability that stood out as key factors influencing acceptance. This speaks to the importance of justice in how people think about access to healthcare innovations. Practical issues like affordability and availability were more influential in shaping acceptance, emphasizing justice in healthcare access.[22]

The importance of autonomy and shared-decision making in gene therapy

Our results point to a common gap between recognition and understanding; people are familiar with the term but lack a clear sense of how gene therapy works. This finding echoes previous research showing that public knowledge of gene therapy is often quite shallow, shaped more by media exposure than by meaningful comprehension.[23] The educational video appeared to help bridge that gap. After watching it, many participants reported to be able to make an informed decision about whether to take gene therapy as a treatment or not. This suggests that even short, well-designed explanations can improve public grasp of complex scientific topics. As Scheufele *et al.* (2019) emphasize, effective public engagement strategies that clearly communicate complex scientific concepts (such as CRISPR or viral vectors) are essential for fostering understanding and building public trust in emerging biotechnologies.[24]

Participants' responses highlighted the importance of autonomy in decision-making. External pressure (whether from family members or doctors) was generally perceived negatively. This reinforces the idea that, for most people, decisions about gene therapy should be left to the individual. In contrast, moral or religious objections had relatively little impact, with nearly half of respondents taking a neutral stance. This may reflect a broader shift towards secular, individualistic approaches to ethics (at least in the population sampled here).[8] However, the role of medical authority came through very clearly, with almost all participants saying that they would rely on their doctor's recommendation. Even when dealing with unfamiliar or experimental treatments, people still place a great deal of trust in healthcare professionals, which raises questions about how informed consent processes are actually experienced in practice. This highlights the importance of shared decision-making, where patients and their clinicians collaboratively consider their treatment options.[25,26] This ensures that patients are well informed about the options available, respects their autonomy and supports ethically sound care.

Gene therapy as a preventive treatment: higher promise, lower public acceptance

In line with the latest research on public attitudes toward gene therapies, our findings indicate a generally positive acceptance.[10,27–30] Specially, acceptance rates are higher in hypothetical vignettes where patients are already symptomatic or have a high likelihood of developing symptoms. Conversely, willingness to accept gene therapy decreases in scenarios when the onset of symptoms remains uncertain. This pattern may reflect the same underlying trend observed in earlier research, where gene therapies receive greater public support when intended for life-threatening conditions, rather than less severe or non-life-threatening cases.[8,28] In both cases, the perceived severity or immediacy of the condition appears to play a key role in shaping attitudes toward treatment. These patterns suggest that gene therapy is predominantly perceived as a curative rather than a preventive treatment. Present and visible suffering triggers stronger moral intuitions than probabilistic reasoning about future illness, suggesting a public discomfort with preventive interventions in the absence of suffering. This aligns with earlier ethical analyses that highlight the centrality of current suffering in public moral reasoning.[31]

Current literature comparing preferences between prevention and cure reveals a wide range of attitudes, including no clear preference between both.[32] Prevention was perceived as more acceptable than cure when aimed for younger individuals, which aligns with our findings showing greater public support for preventative gene therapy treatments in vignettes featuring younger patients.[32] This is also reflected by Persad *et al.* (2009), who describe a utilitarian approach to resource allocation, prioritizing individuals who are expected to gain more life-years or future potential from medical interventions.[33]

Furthermore, existing literature on preventive medicine highlights controversial attitudes, with general practitioners' recommendations emerging as a strong motivator. At the same time, there is notable scepticism towards pharmaceutical companies and academic institutions.[34] Furthermore, some studies caution against treating asymptomatic carriers due to the potential for adverse side effects and the risk of incurring unnecessary healthcare costs.[35] Moreover, Meertens *et al.* (2013) found that treatment interventions tend to receive a greater monetary appreciation than preventive measures,[36] reinforcing the broader trend of higher public support for curative approaches. While gene therapies are not traditionally classified as preventive measures, they may serve a preventive role for individuals diagnosed with a genetic mutation that puts them at risk of developing certain conditions.[37] In such cases, early intervention with gene therapy could potentially delay or prevent disease onset. These findings suggest that for genetic conditions with variable penetrance, accurate risk assessment and prognosis are essential to justify the consideration of gene therapy as a viable option in the early stages of disease. Furthermore, patients' needs and preferences must be considered to ensure gene therapies are developed for those willing to receive them. As Doevendans *et al.* (2022) caution, there is a risk of developing therapies for mildly affected patients who may not even seek them, while leaving severely affected patients without options.[38]

Limitations

The survey was distributed exclusively in Flanders and in Dutch, excluding French- and German-speaking communities. Recruitment through pharmacies and the use of convenience sampling may have introduced selection bias, as participants visiting pharmacies could have higher health awareness or greater receptivity to medical interventions. Additionally, the sample overrepresented Catholic women and predominantly consisted of highly educated individuals, which may have influenced responses related to information and trust in science. Furthermore, the limited sample size reduces generalizability, and reliance on self-reported data may introduce social desirability bias. The informational video was necessarily brief due to the recruitment strategy, focusing primarily on the genetic nature of gene therapies; as a result, detailed information on complex delivery procedures, pre-treatment conditioning, isolation periods, or potential future fertility consequences was not included. These factors may influence participants' perceptions of uncertainty and acceptance and carry ethical and social implications that could vary with the patient's age. We deliberately excluded them to limit survey fatigue and maintain focus on general perceptions of uncertainty associated with gene therapy, but future research could explore these additional aspects to better understand their impact on decision-making and ethical considerations. Additionally, the survey item addressing potential changes to a person's identity may have been interpreted differently by participants, which could affect the precision with which this question captured perceptions of ethical concerns related to gene therapy.

Conclusion

While gene therapy remains unfamiliar to many in Belgium, public attitudes were generally positive, driven more by perceived benefits than by scientific certainty. Most participants believed treatment decision should be autonomously; however they would still heavily rely on their doctor's guidance, highlighting the importance of shared decision-making. Many perceived gene therapy as a curative treatment, with visible suffering prompting stronger support than preventive use in the absence of symptoms.

Disclosures

During the preparation of this work the author(s) used GPT-4o mini in order to improve the readability and language. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Data availability statement

Underlying data

KU Leuven RDR (Dataverse): Replication Data for: Public Perception and Willingness to Accept Somatic Gene Therapy: A Belgian Survey Study. https://doi.org/10.48804/J67GIM.

The project contains the following underlying data[39]:

- Dateset_Excel.xlsx

Extended data

KU Leuven RDR (Dataverse): Replication Data for: Public Perception and Willingness to Accept Somatic Gene Therapy: A Belgian Survey Study. https://doi.org/10.48804/J67GIM.[39]

The project contains the following extended data:

- Questionnaire.docx
- Video_genetherapy.mp4
- Readme.txt

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

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Open Peer Review

Current Peer Review Status: ✔ ✔ ✔ ✔ ?

Version 4

Reviewer Report 15 May 2026

https://doi.org/10.21956/openreseurope.25624.r73456

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?

Tao Huang
Chinese Academy of Sciences Shanghai Institute of Nutrition and Health, Shanghai, Shanghai, China

The authors enrolled 289 participants, of whom 67% had completed higher education, 64% had children, and 87% had heard of gene therapy before. They found that overall willingness was high. Attitudes were generally positive, with limited concerns about its experimental features. However, key barriers included fears of altered identity (39%), external pressure (38%), and skepticism about its novelty (31%). This is an important work to know public perceptions and willingness to accept somatic gene therapy. There are several problems:

1. The sample size was too small. More participants from diverse backgrounds and countries should be included.
2. The authors should specify the somatic gene therapy, since different somatic gene therapies have different risks.
3. On https://rdr.kuleuven.be/dataset.xhtml?persistentId=doi:10.48804/J67GIM and https://rdr.kuleuven.be/dataset.xhtml?persistentId=doi:10.48804/J67GIM, Dataset_Excel.xlsx was locked. The authors should remove the identity and make the data publicly available.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and does the work have academic merit?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Bioinformatics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 07 May 2026

https://doi.org/10.21956/openreseurope.25624.r73278

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Eva-Maria Merz
Vrije Universiteit Amsterdam, Sanquin, The Netherlands

I think the authors have done a good job and addressed all open points adequately. I have nor further comments.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 30 April 2026

https://doi.org/10.21956/openreseurope.25624.r73277

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Sharon Phares
Tufts Medical Center, Boston, Massachusetts, USA

Thank you for addressing the comments on the initial version

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: healthcare system design, cell & gene therapies, primary care, health services research

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 3

Reviewer Report 25 March 2026

https://doi.org/10.21956/openreseurope.25342.r71259

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Eva-Maria Merz
Vrije Universiteit Amsterdam, Sanquin, The Netherlands
Louisanne van Hooff
Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

- In the abstract, under Results, a space is missing between ‘long-term effects (8%),’ and ‘and uncertain’.
- In the introduction on page 4, the second paragraph, I want to suggest to the authors to refer to Krishanmurti et al. (2026) ‘Informed shared decision-making or rigid eligibility and exclusion criteria for gene therapy for sickle cell disease?’ as a nice complementary example of the challenges that go with inclusion and exclusion criteria and eligibility considerations.
- In the methods section on page 5, in the second to last sentence of the first paragraph, a word is probably missing after ‘modification of genetic’.
- On page 5, the authors explain that the fourth section of the survey was based on previous research on ethical considerations that influenced acceptability of GT. Currently, I do not understand the choice for the question ’. I do see that it is based on previous literature by Robillard et al. and Wang et al., but what do the authors mean with a change in a person’s identity/personality? This question can be interpreted in so many different ways by a survey participant, that I’m wondering if this question measures what the authors want to know.
- In the methods section on page 5 under Participant recruitment, the authors explain that participants were recruited through three local pharmacies, and in the limitations section, attention has been addressed to the bias this might have introduced due to a possible higher health awareness and greater receptivity to medical interventions. However, it is still unclear why the authors opted for recruitment through local pharmacies in the first place. What was the rationale behind this?
- In the rebuttal letter to the second reviewer, the authors shared their rationale behind choosing the ages 5, 20 and 65. It would benefit the paper to add the rationale behind these

ages in the main text as well.

- In table 3 on page 7, the word choice in the scaling from 'strongly disagree' to 'strongly agree' does not make sense in combination with the statements in column 1. The statements cannot be answered with a '(dis)agreement'. It seems a question prompted like 'would you agree or disagree with a gene therapy in the following cases?' or something along those lines was asked on the survey, but the reader does not know that right now. Providing extra information on the prompts or wording of these questions or the scaling is necessary. Additionally, the third to last and second to last statements in the first column, currently are exactly the same. I think the wording in the third to last statement was also intended to be 'Doctors expect future issues' instead of 'It is uncertain whether symptoms will develop.' This needs to be corrected.
- On page 9, the authors start the second full paragraph with 'Autonomy was another recurring theme.' No themes are mentioned earlier in the piece, and the methods section does not mention a thematic analysis or anything similar. What do the authors mean with this?
- From the rebuttal letter to the second reviewer, I understand that the authors decided to not include side effects and symptoms, as the goal of the study was to look at perceptions of associated uncertainty and to limit survey fatigue. However, to measure acceptance and perceptions of uncertainty, it would have been very interesting to include information in the video, or a question in the survey on the conditioning that takes place in advance of a GT, on the isolation period, and on the risk of possible future (in)fertility. Moreover, these also fall under ethical considerations, as they carry moral and social consequences of which the importance might shift with a (hypothetical) patient's age. It might be necessary to better argue why these topics were not included in the video/survey, or add it to the limitations section of the discussion on page 10, in more detail.
- On page 10, the authors mentioned using GTP-4o mini, but I think they meant GPT-4o mini.
- In the questionnaire that is shared on KU Leuven RDR (Dataverse) on page 3 and page 5, there are questions that were not translated from Dutch to English.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and does the work have academic merit?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 10 Apr 2026

Phaedra Locquet

We thank the reviewer for their careful and thorough review. We have considered all feedback and addressed each point below, incorporating the suggested revisions to improve the manuscript.

In the abstract, under Results, a space is missing between 'long-term effects (8%),' and 'and uncertain'.
Thank you, we corrected that typo.

In the introduction on page 4, the second paragraph, I want to suggest to the authors to refer to Krishanmurti et al. (2026) 'Informed shared decision-making or rigid eligibility and exclusion criteria for gene therapy for sickle cell disease?' as a nice complementary example of the challenges that go with inclusion and exclusion criteria and eligibility considerations.

Thank you for this helpful suggestion. We agree that this recent paper provides a relevant and concrete illustration of the ethical and methodological tensions surrounding inclusion, exclusion, and eligibility criteria in gene therapy trials. We have now incorporated a reference to Krishanmurti et al. (2026) in the second paragraph of the Introduction (p.4) to complement our introduction with this example from sickle cell disease.

In the methods section on page 5, in the second to last sentence of the first paragraph, a word is probably missing after 'modification of genetic'.

Thank you for pointing this out. We have revised the sentence for clarity.

On page 5, the authors explain that the fourth section of the survey was based on previous research on ethical considerations that influenced acceptability of GT. Currently, I do not understand the choice for the question '. I do see that it is based on previous literature by Robillard et al. and Wang et al., but what do the authors mean with a change in a person's identity/personality? This question can be interpreted in so many different ways by a survey participant, that I'm wondering if this question measures what the authors want to know.

Thank you for this comment. We would like to clarify that the question on changes to a person's identity or personality was intended to capture participants' perceptions or beliefs about the potential impact of gene therapy, not to suggest that gene therapy can actually alter personality. This approach follows prior studies by Robillard et al. and Wang et al., which similarly explored public perceptions of ethical implications related to personal characteristics in genetic interventions. We acknowledge that participants may interpret this item in slightly different ways, reflecting the complexity of assessing attitudes toward hypothetical scenarios. We have added it to the limitations section: *"The survey item addressing potential changes to a person's identity or personality may have been interpreted differently by participants, which could affect the precision with which this question captured perceptions of ethical concerns related to gene therapy."*

In the methods section on page 5 under Participant recruitment, the authors explain that participants were recruited through three local pharmacies, and in the limitations section, attention has been addressed to the bias this might have introduced due to a possible higher health awareness and greater receptivity to medical interventions. However, it is still unclear why the authors opted for recruitment through local pharmacies in the first place. What was the rationale behind this? Thank you for this observation. Participants were recruited through local pharmacies as a pragmatic and accessible setting within the Belgian healthcare system, where community pharmacies serve a broad and diverse segment of the population, allowing efficient recruitment within a limited timeframe. In the rebuttal letter to the second reviewer, the authors shared their rationale behind choosing the ages 5, 20 and 65. It would benefit the paper to add the rationale behind these ages in the main text as well.

Thank you for this helpful suggestion. We have now added the rationale for selecting the ages 5, 20, and 65 years in the Methods section. It reads as follows: *"The chosen age groups were based on the case design of Ormondroyd et al. (2024), who used ages 5, 20, and 50 years, with 50 being replaced by 65 years to better capture differences in life stage, responsibilities, and social context."*

In table 3 on page 7, the word choice in the scaling from 'strongly disagree' to 'strongly agree' does not make sense in combination with the statements in column 1. The statements cannot be answered with a '(dis)agreement'. It seems a question prompted like 'would you agree or disagree with a gene therapy in the following cases?' or something along those lines was asked on the survey, but the reader does not know that right now. Providing extra information on the prompts or wording of these questions or the scaling is necessary. Additionally, the third to last and second to last statements in the first column, currently are exactly the same. I think the wording in the third to last statement was also intended to be 'Doctors expect future issues' instead of 'It is uncertain whether symptoms will develop.' This needs to be corrected.

We have added the questions indicating how the agree/disagree scale should be interpreted. It reads now as follows: *Shading in the tables is used to visualize regions with the greatest participant density (percentage of participants). Results related to the following question: "In the following statements, indicate the extent to which you agree with the*

consideration to undergo gene therapy, taking into account the age and stage of the disease.". **Additionally, we thank the reviewer for catching this error in the table, which has since been corrected. The statements have also been revised in line with your suggestions.**

On page 9, the authors start the second full paragraph with 'Autonomy was another recurring theme.' No themes are mentioned earlier in the piece, and the methods section does not mention a thematic analysis or anything similar. What do the authors mean with this?

Thank you for pointing this out. We have revised the paragraph for clarity and now describe the findings directly in terms of participants' responses rather than referring to "themes." The revised sentence reads: "*Participants' responses highlighted the importance of autonomy in decision-making*." This avoids any confusion about thematic analysis while accurately reflecting the data.

From the rebuttal letter to the second reviewer, I understand that the authors decided to not include side effects and symptoms, as the goal of the study was to look at perceptions of associated uncertainty and to limit survey fatigue. However, to measure acceptance and perceptions of uncertainty, it would have been very interesting to include information in the video, or a question in the survey on the conditioning that takes place in advance of a GT, on the isolation period, and on the risk of possible future (in)fertility. Moreover, these also fall under ethical considerations, as they carry moral and social consequences of which the importance might shift with a (hypothetical) patient's age. It might be necessary to better argue why these topics were not included in the video/survey, or add it to the limitations section of the discussion on page 10, in more detail.

Thank you for this suggestion. We have added a note to the limitations section acknowledging that the video and survey did not include information on pre-treatment conditioning, isolation periods, or potential impacts on future fertility. We briefly explain that these topics were deliberately excluded to limit survey fatigue and maintain focus on general perceptions of uncertainty associated with gene therapy, while noting that future research could explore these factors in more detail. *"The informational video was necessarily brief due to the recruitment strategy, focusing primarily on the genetic nature of gene therapies; as a result, detailed information on complex delivery procedures, pre-treatment conditioning, isolation periods, or potential future fertility consequences was not included. These factors may influence participants' perceptions of uncertainty and acceptance and carry ethical and social implications that could vary with the patient's age. We deliberately excluded them to limit survey fatigue and maintain focus on general perceptions of uncertainty associated with gene therapy, but future research could explore these additional aspects to better understand their impact on decision-making and ethical considerations."*

On page 10, the authors mentioned using GTP-4o mini, but I think they meant GPT-4o mini. Thank you, we corrected that typo. In the questionnaire that is shared on KU Leuven RDR (Dataverse) on page 3 and page 5, there are questions that were not translated from Dutch to English.

Thank you, we have made the necessary translations.

Competing Interests: No competing interests were disclosed.

Version 2

Reviewer Report 19 February 2026

https://doi.org/10.21956/openreseurope.24792.r68978

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Karine Dube
University of Pennsylvania, Pennsylvaniaia, Pennsylvania, USA

Overall Assessment:
This is a timely cross-sectional study on public perceptions and willingness to accept somatic gene therapy in Belgium. The study is well constructed, and the paper is clearly written. The tables, including heat maps of the results, are well designed. Only minor comments are noted. This reviewer recommends indexing after minor revisions.

Major:

- Did the authors consider including bivariate and multivariate analyses as well?
- There are several mentions of gene therapy as a treatment, but not as a cure. Should this distinction be clarified or reconciled?

Minor:

- Title: Should “perceptions” be plural?
- Abstract, Results: Ensure extra spacing between “),” and “and.”
- Abstract, Results, last sentence: Please check syntax and completeness: “Patients’ age played a secondary role, with younger individuals generally received higher support for gene therapy than older adults.” Should “received” be “receiving”?
- Methods, Participant Recruitment: “participants that” should be “participants who.”
- Results, A Socio-Demographic Characteristics: “individuals that” should be “individuals who.”
- Results, second paragraph: Consider replacing “felt” with “were” [unable to explain it]. It is difficult to determine what survey respondents *feel*.
- Results, 2. Patient Profiles: The word “in” between “28.1%” and “expressing” is unnecessary.
- Discussion, first sentence: Consider adding “To our knowledge, this survey is the first…” [acknowledging that there have been similar surveys in other settings].
- This reviewer recommends a careful final review of grammar, syntax, and punctuation.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and does the work have academic merit?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Socio-behavioral sciences

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 10 Mar 2026

Phaedra Locquet

We thank the reviewer for the careful evaluation of our manuscript. We have addressed each comment in detail, and our responses are presented below.
1. We did consider including bivariate and multivariate analyses; however, given the limited sample size, we decided not to perform these analyses to avoid Type-1 mistakes.
2. We adapted a part in the introduction, in which we clearly mention the distinction between treatment & cure, as illustrated below. We decided to not present gene therapy as a cure to the participants because at this moment it remains debatable if one could consider GT as a cure: “Although gene therapy is most often presented as a cure, this framing remains debated given limited long-term follow-up data. Nevertheless, its effects are currently considered potentially durable.
3. We thank the reviewer for the suggestion to improve the reading of our manuscript. We have carefully considered all remarks and have incorporated them into the revised version.

Competing Interests: No competing interests were disclosed.

Reviewer Report 13 February 2026

https://doi.org/10.21956/openreseurope.24792.r68898

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Marilyn Baffoe-Bonnie
University of Pennsylvania, Pennsylvania, Pennsylvania, USA

Thank you for taking the time to carefully address these comments. The manusript can now be indexed.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am an ELSI (Ethical, Legal, and Social Implications of Genetics and Genomics) researcher, with a focus on the lived experiences of individuals undergoing gene therapy and the integration of this therapy into clinical practice.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 30 January 2026

https://doi.org/10.21956/openreseurope.24792.r68899

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Sharon Phares
Tufts Medical Center, Boston, Massachusetts, USA

Thank you for making the suggested changes. The article is interesting and will add to the field.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I have done research and published extensively in the area of gene therapy.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 18 December 2025

https://doi.org/10.21956/openreseurope.23216.r63845

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?

Marilyn Baffoe-Bonnie
University of Pennsylvania, Pennsylvania, Pennsylvania, USA

Overall Comments
This was a well-conducted study on an increasingly important topic as gene therapy enters health care spaces. A few minor changes are warranted to clarify the study methods and situate it alongside scholarship on how gene therapy is described.

Introduction
While the authors accurately note that gene therapy is often described as curative, they may consider briefly acknowledging the ongoing debate in the literature about the appropriateness of this framing.

Methods
A bit more detail would be helpful to understand whether individuals were presented with information about gene therapy in general or regarding specific conditions. The delivery process for gene therapy varies widely, especially across different conditions, with some requiring significantly more complex procedures (e.g., chemotherapy, extended hospitalizations) compared to others (e.g., those performed in outpatient settings). Additionally, the mechanisms for gene therapy (e.g., gene addition, gene correction, gene silencing) vary widely, which may also change perceptions.

It was unclear what symptoms, long-term effects, and side effects were presented. Again, these vary across conditions and may impact perceptions of willingness to accept gene therapy.

Why were 5, 20, and 65 chosen as the ages?

Limitations
Since recruitment occurred in pharmacies, participants may not fully represent the broader public. Individuals visiting pharmacies may have higher health awareness or greater receptivity to medical interventions, which could potentially influence their responses.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and does the work have academic merit?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am an ELSI (Ethical, Legal, and Social Implications of Genetics and Genomics) researcher, with a focus on the lived experiences of individuals undergoing gene therapy and the integration of this therapy into clinical practice.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 20 Jan 2026

Phaedra Locquet

We thank the reviewer for the careful evaluation of our manuscript. We have addressed each comment in detail, and our responses are presented below.

1. We agree that the use of the term 'curative' is debated in the literature and that long-term evidence is still limited. We have therefore adjusted the wording in the manuscript to reflect this nuance, noting that gene therapy is often presented as curative while emphasizing its potentially durable, and briefly acknowledging the ongoing discussion around this framing. *"Although gene therapy is most often presented as a curative treatment, a framing that remains debated given limited long-term follow-up, its effects are currently considered potentially durable, and attitudes towards its preventive use remain unclear."*
2. We have added additional details related to the provided information to the Methods section, as follows: *"More specifically, the animated video provided information on the nature and modification of genetic and the origin of genetic disorders. It also explained how gene therapy targets the genetic mutation, the use of (viral) vectors and the therapeutic aim of the treatment."* However, we did not provide extensive details on the mechanisms underlying gene therapy or on more complex aspects of the intervention. While we acknowledge that this information is important, we aimed to keep the informational video as concise as possible due to the recruitment strategy, which limited the opportunity to include more in-depth explanations. Therefore we focussed on the genetic nature of the intervention in a broad sense. We have now also included this in the limitations of the study, as follows: *"Additionally, the informational video was necessarily brief due to the recruitment strategy, focusing primarily on the genetic nature of gene therapies. As a result, detailed information on complex delivery procedures and gene therapy mechanisms was not included, which may have influenced participants' perceptions."*

3. We agree that information related to symptoms, side-effects, was missing from the paper. Therefore, we have added, for each table, the specific case that was presented to the participants when answering. These cases clearly described the impact of the symptoms. One example is provided below: *"Results related to the following case: "Suppose you have a genetic disease. The symptoms of your illness strongly affect your daily life. You experience difficulties performing household tasks, have problems with mobility, face limitations in social activities, and you are unable to sustain a full workday. Your condition also worsens with age, increasingly impacting your life. There is now a new gene therapy available which, as the only treatment, can stop the progression of your disease. However, because this therapy is new, scientists still know little about its effectiveness, long-term effects, and possible side effects."* However, as this paper aimed to gain a broader understanding of participants' perceptions of gene therapy, we did not include specific side effects in order to limit the number of survey questions and associated survey fatigue. Moreover, we specifically aimed to assess their perceptions of the associated (long-term) uncertainty of these therapies.
4. We followed the case design of Ormondroyd et al. (2024), who used cases involving individuals aged 5, 20, and 50 years. After discussion within the research team, we decided to include an age level of 65 years instead of 50 years to better reflect greater differences in life stage, particularly in terms of responsibilities and social context.
5. We agree that recruiting participants through pharmacies may not fully capture the perspectives of the broader public, as these individuals might have higher health awareness or greater receptivity to medical interventions. We have added a note in the limitations section acknowledging this potential source of selection bias. We have added the following text to the limitations: *"Recruitment through pharmacies and the use of convenience sampling may have introduced selection bias, as participants visiting pharmacies could have higher health awareness or greater receptivity to medical interventions. Additionally, the sample overrepresented Catholic women and predominantly consisted of highly educated individuals, which may have influenced responses related to information and trust in science."*

Competing Interests: No competing interests were disclosed.

Reviewer Report 20 November 2025

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Sharon Phares
Tufts Medical Center, Boston, Massachusetts, USA

This was a solid paper on a very interesting topic. A few minor changes are warranted:

1) In the introduction the authors mention low clinical trial participation without the primary reason - that these therapies almost always target very small populations, many of whom have huge time delays in obtaining a diagnosis and are often faced with life-threatening disease.
2) Additionally, the statement that 'gene therapy is most often presented as a curative treatment' is more the media presenting them this way. More accurately, they should be presented as durable in effect but there has not been enough time for patient follow-up to claim 'curative' in the lifetime sense.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and does the work have academic merit?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I have done research and published extensively in the area of gene therapy.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 20 Jan 2026

Phaedra Locquet

We thank the reviewer for the careful evaluation of our manuscript. We have addressed each comment in detail, and our responses are presented below.

1. We agree that the small size of target populations and delays in diagnosis are primary drivers of low clinical trial participation in gene therapy. We have revised the introduction to explicitly acknowledge these factors before discussing additional ethical and methodological challenges related to trial participation and inclusion criteria. The text now reads as follows: *“Because many gene therapies target very small, rare disease populations, and because these patients often experience significant delays in*

obtaining an accurate diagnosis while facing life-threatening conditions, clinical trial recruitment is inherently limited. Beyond these structural constraints, low participation in clinical trials remains persistent, as many eligible individuals hesitate due to unknown long-term effects, adverse side effects, and the therapy's experimental status."

2. We agree that it is premature to characterize gene therapies as definitively 'curative' in a lifetime sense, given the limited long-term follow-up. We have revised the manuscript to describe these therapies as having potentially durable effects, rather than as curative. *"Although gene therapy is most often presented as a curative treatment, a framing that remains debated given limited long-term follow-up, its effects are currently considered potentially durable, and attitudes towards its preventive use remain unclear."*

Competing Interests: No competing interests were disclosed.