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Patient preferences for gene therapy in haemophilia: Results from the PAVING threshold technique survey

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Abstract

Objectives: The aim of the Patient preferences to Assess Value IN Gene therapies (PAVING) study was to investigate trade-offs that adult Belgian people with haemophilia (PWH) A and B are willing to make when choosing between prophylactic factor replacement therapy (PFRT) and gene therapy.

Methods: The threshold technique was used to quantify the minimum acceptable benefit (MAB) of a switch from PFRT to gene therapy in terms of 'Annual bleeding rate' (ABR), 'Chance to stop prophylaxis' (STOP), and 'Quality of life' (QOL). The design was supported by stakeholder involvement and included an educational tool on gene therapy. Threshold intervals were analysed using interval regression models in Stata 16.

Results: A total of 117 PWH completed the survey. Mean thresholds were identified for all benefits, but substantial preference heterogeneity was observed; especially for the STOP thresholds, where the distribution of preferences was bimodal. Time spent on the educational tool and residence were found to impact MAB thresholds. The most accepted (88% of PWH) gene therapy profile investigated in this study comprised of zero bleeds per year (vs. six for PFRT), 90% chance to stop prophylaxis, no impact on QoL, and 10 years of follow-up on side effects (vs. 30 for PFRT).

Conclusions: Results from this study proved the value of educating patients on novel treatments. Moreover, preference heterogeneity for novel treatments was confirmed in this study. In gene therapy decision-making, preference heterogeneity and the impact of patient education on acceptance should be considered.

KEYWORDS
gene therapy, haemophilia, perspectives, preference, questionnaire, survey

1 | INTRODUCTION

Market access of gene therapies is complicated by limited clinical evidence, uncertainty in long-term safety and efficacy, and high prices.[1–4] Gene therapies are challenging standard health technology assessment (HTA) practices due to these uncertainties and their unique attributes (e.g., long-term benefits).[5–12] While no gene therapy-specific value framework exists,[13] it has been argued that factors beyond health gain should be considered such as value of cure versus incremental benefits, while also addressing the uncertainty in long-term effects.[5,7,9,14,15] Patient preferences can be elicited to quantify the importance of these new elements and inform value propositions for marketing authorization and reimbursement applications.[15,16] Especially for innovative products and products for rare diseases, the patient perspective is believed to be crucial.[17–20]

One of the rare diseases for which AAV-based gene therapies are in late development is haemophilia (A and B). While these gene therapies come with the promise of a cure where one infusion could possibly replace lifelong administration of other high-cost treatment options, duration of effect of these gene therapies is uncertain. Current standard of care for moderate to severe haemophilia consists of regular invasive intravenous administrations of coagulation factor (prophylactic factor replacement therapy, PFRT), resulting in fluctuations of achieved factor levels that make people with haemophilia (PWH) more prone to bleeds and joint damage, and may result in development of inhibitors in some PWH.[21–24]

The aim of our Patient preferences to Assess Value IN Gene therapies (PAVING) study was to investigate trade-offs that adult Belgian PWH A and B make when asked to choose between a standard of care (PFRT) and AAV-based gene therapy. Other treatments such as non-factor replacement therapies (e.g., emicizumab) were not considered.

KEY POINTS FOR DECISION MAKERS

- Preferences for gene therapy in haemophilia are remarkably heterogenous.
- Patient education on gene therapies impacts patient acceptance.
- Geographical differences in preferences for gene therapies exist.
- Preference heterogeneity should be considered in regulatory and payer decision making.

2 | METHODS

2.1 | Survey design

The protocol for this study has been published elsewhere[25] and described an eight-step approach that was taken in the survey design. The threshold technique[26] was chosen as preference elicitation method. Interviews with PWH were conducted, results have been published elsewhere,[27] to select attributes for the survey. The selected attributes 'Annual bleeding rate' (ABR), 'Chance to stop prophylaxis' (STOP), 'Time that side effects have been studied' (TIME), and 'Quality of life' (QOL) were included in labelled (PFRT vs. gene therapy) threshold technique questions that formed a response logic. Respondents first answered a baseline question (Figure 1) and then answered three benefit-specific series of threshold questions in which only the respective benefit was systematically varied until a level of the attribute was reached that induced a switch in the respondent's choice (from gene therapy to PFRT, or vice versa). From this switch, an interval was identified within which their threshold lied that offset the other differences in attribute levels between PFRT and gene therapy, representing participants' individual relative minimum acceptable benefit (MAB). The relative MAB represents the additional benefit that gene therapy needs to provide in comparison to PFRT to induce a switch from PFRT to gene therapy. The TIME levels (30 years for PFRT and 10 years for gene therapy) were held constant throughout the questions. As knowledge of participants on gene therapy was expected to be limited and hypothesized to influence acceptance of gene therapy, an educational tool informed participants on gene therapy before they were asked threshold technique questions.[25] The design process was supported by stakeholder and patient involvement.

2.2 | Patient recruitment

Ethical approval was obtained from the Medical Ethics Committee of UZ KU Leuven/Research in Belgium (S63686). PWH diagnosed with moderate to severe haemophilia A or B of 18 years or older and living in Belgium were recruited through three national haemophilia reference centres (UZ Leuven, Cliniques Universitaires Saint-Luc-UCLouvain, and Hôpital Universitaire des Enfants Reine Fabiola) and the national patient organization (AHVH) in Belgium. Recruiting parties sent an initial invitation with link to the survey via e-mail or newsletters to possible participants in their native language between the 20th and 23rd of April 2020. A reminder was sent by all recruiting parties between the 5th and 11th of May 2020. PWH could participate between April 2020 and May 2020 on an anonymous basis and were not compensated for their participation.

2.3 | Data cleaning

Responses of participants were compared across questions to identify ineligible participants and inconsistencies. Entries were excluded from analysis if participants reported no or mild haemophilia, were under 18 years old, did not live in Belgium, completed less than 50% of the survey, or failed two or more validity checks. Validity checks consisted of a comprehension question similar to that of Mansfield et al.,[28] time to complete the survey (< 10 min), and choice consistency. From identified doubles, the most complete or latest entry was included in analysis.

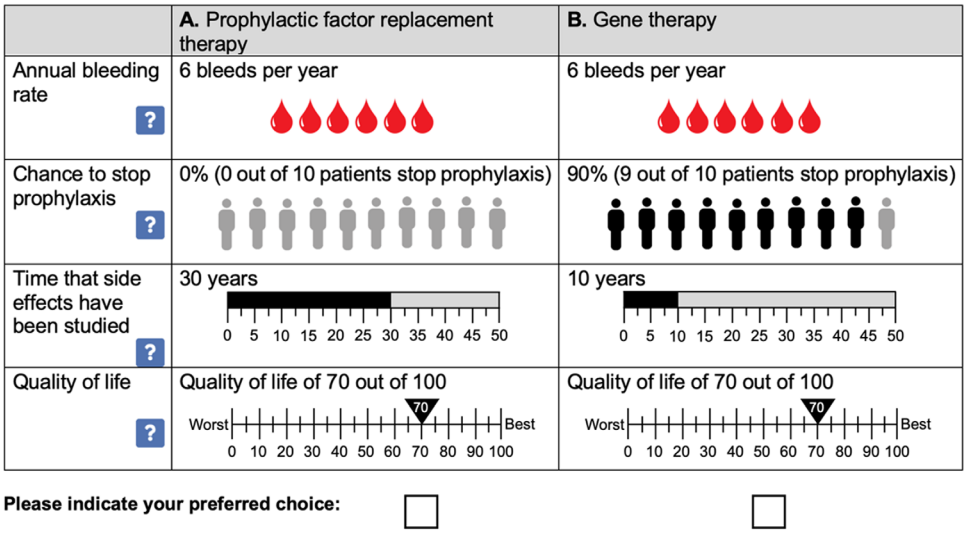

FIGURE 1 First threshold technique question showing the baseline attribute levels included in the survey

2.4 | Analysis

Descriptive statistics were used to report on participant characteristics. Health literacy scores were calculated using the approach of Fransen et al.[29] Participants' QoL scores, reported on the EQ5D Visual Analogue Scale (VAS), were regressed against participant characteristics to identify predictors of self-reported QoL. Threshold intervals were analysed per attribute using two interval regression (Tobit) models: (1) a constant-only model to identify the mean threshold (MAB) across the sample, and (2) a covariate-adjusted model to explore whether and how participant characteristics influence the MAB. Participant characteristics of interest for the covariate-adjusted model were identified prior to analysis and were selected based on correlation tests between these covariates (Supporting information I).

The constant-only interval regression model for benefit b (b ∈ [ABR, STOP, QOL]) was specified as follows:

$$Threshold_b = constant_b$$

And the covariate-adjusted interval regression model for benefit b (b ∈ [*ABR*, *STOP*, *QOL*]) was specified as follows:

$$Threshold_b = cons\tan t_b + \beta_1 Cov1_i + \beta_2 Cov2_i + \beta_x CovX_i \ldots + \varepsilon_{br}$$

where $constant_b$ is the mean threshold of benefit $b(b \in [ABR, STOP, QOL])$ when all other covariates would be set to zero, and ε_{br} is an independent and identically normally distributed random error term with mean 0 and variance σ^2. The coefficients (β) capture the effect of the presence or absence of each individual characteristics on MAB. Cov1, Cov2, and CovX represent characteristics of participant *i*. For all statistical analyses, Stata 16 was used and a *P*-value ≤ .05 was considered to be statistically significant.

3 | RESULTS

3.1 | Patient sample

Data were collected between the 20th of April and 22nd of May 2020. Haemophilia reference centres invited 235 PWH, and the patient organization invited all PWH in their database. Based on data provided by the patient organization, the total eligible population in Belgium was estimated to count 449 PWH. From 220 entries, 117 were found to be eligible (all with 100% survey completion). Other entries were excluded as participants completed < 50% of the survey ($n = 85$), reported no or mild haemophilia, were under age, or failed two validity checks ($n = 1$). In addition, three doubles were identified and removed.

Participant characteristics were patient-reported and are presented in Table 1. The median age of the sample was 51. Most participants lived in Flanders and participated through their haemophilia reference centre. Most suffered from haemophilia A (84%), reflecting prevalence rates in the eligible Belgian PWH population (82% A, 18% B).[30] The majority reported to have severe haemophilia (82%) and to receive PFRT (63%). Six participants (5%) had received gene therapy. PFRT administration frequency was higher for PWH A than B ($P = .001$) and severe than moderate haemophilia ($P = .024$). Across the full sample, the median ABR was six, the median number of damaged joints (i.e., target joints, or the number of joints reported by participants to be affected due to haemophilia complications) was four, and the median QoL score was 73. Most participants had already discussed gene therapy treatment with their clinician (56%). Self-reported knowledge on gene therapy varied, and most participants had adequate health literacy (90%).

Only the number of damaged joints was found to be a significant predictor of QoL (coef. = -1.870, $P = .000$) when regressing self-reported QoL scores against ABR, the number of damaged joints, haemophilia type, disease severity, residence, and presence of inhibitors. Age was

TABLE 1 Participant characteristics (self-reported)

Characteristics		Participants (n = 117)	
		n	%
Sex			
	Males	116	99%
	Females	1	1%
Age, years			
	18–25	11	9%
	26–40	27	23%
	41–60	50	43%
	>60	29	25%
Residence			
	Flanders	77	66%
	Wallonia	28	24%
	Brussels	12	10%
Recruitment source (not self-reported)			
	Haemophilia reference centre	94	80%
	Patient organization	13	11%
	Pretesting	10	9%
Type of haemophilia			
	A	98	84%
	B	19	16%
Disease severity			
	Moderate	21	18%
	Severe	96	82%
Treatment regimen			
	Prophylactic FRT	74	63%
	On-demand FRT	27	23%
	Intensive FRT	0	0%
	Emicizumab	17	15%
	Gene therapy	6	5%
	Other	2	2%
Administration frequency (prophylactic)			
	0–2/month	3	3%
	3–5/month	13	11%
	6–10/month	27	23%
	>10/month	31	26%
Presence of inhibitors			
	Yes	2	2%
	No	115	98%
Treatment satisfaction			
	Very satisfied	56	48%
	Satisfied	52	44%
	Neutral	6	5%
	Unsatisfied	3	3%
	Very unsatisfied	0	0%
Bleeding frequency			
	<12/year	89	76%
	1–5/month	25	21%
	>1/week	3	3%
Number of damaged joints			
	0 joints	10	9%
	1–3 joints	47	40%
	4–6 joints	30	26%
	>6 joints	30	26%
Severity of joint damage			
	Mild	5	4%
	Moderate	34	29%
	Severe	68	58%
Knowledge on gene therapy			
	Very good	13	11%
	Good	22	19%
	Reasonable	49	42%
	Bad	28	24%
	Very bad	5	4%
Discussed gene therapy with clinician			
	Yes	65	56%
	No	52	44%
Gene therapy decision			
	GT in clinical trial	11	9%
	GT outside clinical trial	2	2%
	Not receive gene therapy	17	15%
	No decision	35	30%
Employment status			
	Full-time employed	55	47%
	Part-time employed	11	9%
	Unemployed	10	9%
	Retired	32	27%
	Student	9	8%

(Continues)

TABLE 1 (Continued)

Characteristics		Participants (n = 117)	
		n	%
QoL score			
	80–100	42	36%
	60–79	47	40%
	<60	28	24%
Health literacy			
	Adequate health literacy	105	90%
	Inadequate health literacy	12	10%

also a covariate of interest but was correlated with the number of damaged joints (Spearman's rho = .535, P = .000). In a similar regression model that replaced number of damaged joints with age, age was identified as the only predictor of QoL (coef. = -.282, P = .010). In both models, ABR was not identified as predictor (Figure 2).

3.2 | Mean thresholds and preference heterogeneity

The threshold technique revealed mean thresholds (Figure 3A-E) and thresholds at which most participants would prefer gene therapy (Figure 3B-F). Substantial preference heterogeneity was observed. For both benefit attributes ABR and STOP, preference heterogeneity was observed as an almost bimodal distribution of thresholds.

The ABR threshold series revealed that, on average, participants would accept an additional 1.265 (SE = 1.137) bleeds each year for a gene therapy that would yield a 90% chance to stop prophylaxis, no impact on QoL and of which side effects had been studied for 10 years (vs. 30 for PFRT). If under these conditions gene therapy would result in an ABR of 0 (vs. six for PFRT), 88% of participants would prefer gene therapy and 12% would not. Moreover, 61% would still prefer gene therapy if it would result in the same ABR as PFRT (ABR = 6).

The STOP threshold series identified that, on average, participants required 65.251% (SE = 7.724) chance to stop prophylaxis to accept a gene therapy that would not impact ABR nor QoL and of which side effects had been studied for 10 years (vs. 30 for PFRT). If under these conditions gene therapy would yield 100% chance to stop prophylaxis, 68% of participants would, and 32% would not, prefer gene therapy. Also, 29% would still prefer gene therapy even if the chance to stop prophylaxis would be less than 20%.

The QOL series revealed that, on average, participants require an additional 1.010 (SE = 2.359) QoL points to accept a gene therapy that would not impact ABR, would yield a 90% chance to stop prophylaxis, and of which side effects had been studied for 10 years (vs. 30 for PFRT). If under these conditions gene therapy would result in a QoL score of 100 (vs. 70 for PFRT), 87% of participants would, and 13% would not, prefer gene therapy. Moreover, 61% of participants would still prefer gene therapy if it would result in the same QoL as PFRT (QOL = 70).

3.3 | Factors contributing to preference heterogeneity

Covariate-adjusted interval regression models were used to investigate effect of participant characteristics on their MAB thresholds (Table 2). Across these models, the effect of type of haemophilia, severity of haemophilia, recruitment source, and choice consistency were never significant. Participants' ABR only had an effect on the ABR threshold, with participants with higher ABR tolerating higher numbers of additional bleeds. Age and correct response to the comprehension question only had significant effects on the STOP threshold, with older participants and participants with incorrect comprehension requiring higher chances to stop prophylaxis from gene therapy. Time spent on the educational tool had a significant effect on both the ABR and QOL threshold, with participants spending more time on the tool tolerating more additional bleeds and reductions in QoL. Residence had a significant effect on all MAB, with participants living in the south (Wallonia) requiring more benefit than participants living in the north (Flanders) to switch to gene therapy (Supporting information II).

Participants that never accepted gene therapy throughout the survey made up 8% (n = 9) of the sample. In a logit model that regressed this behaviour against ABR, age, haemophilia type, disease severity, recruitment source, residence, time on the educational tool, and comprehension, no consistent predictor was identified. However, two of

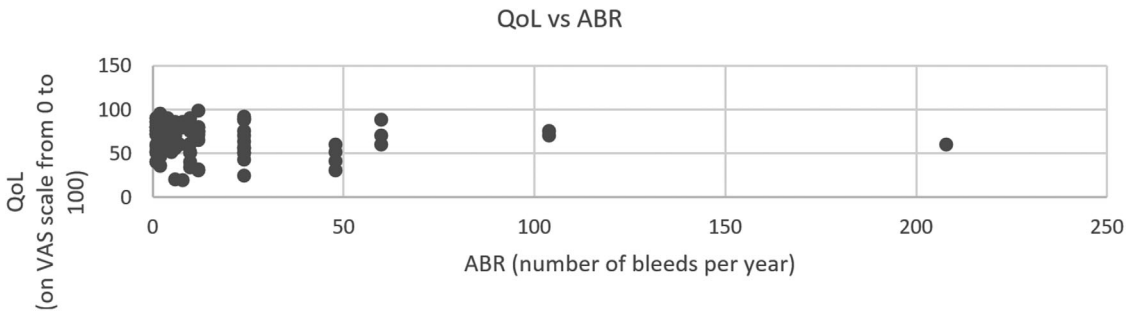

FIGURE 2 Plotting of participants' self-reported QoL scores versus ABR. Abbreviations: ABR, annual bleeding rate; VAS, Visual Analogue Scale; QoL, quality of life

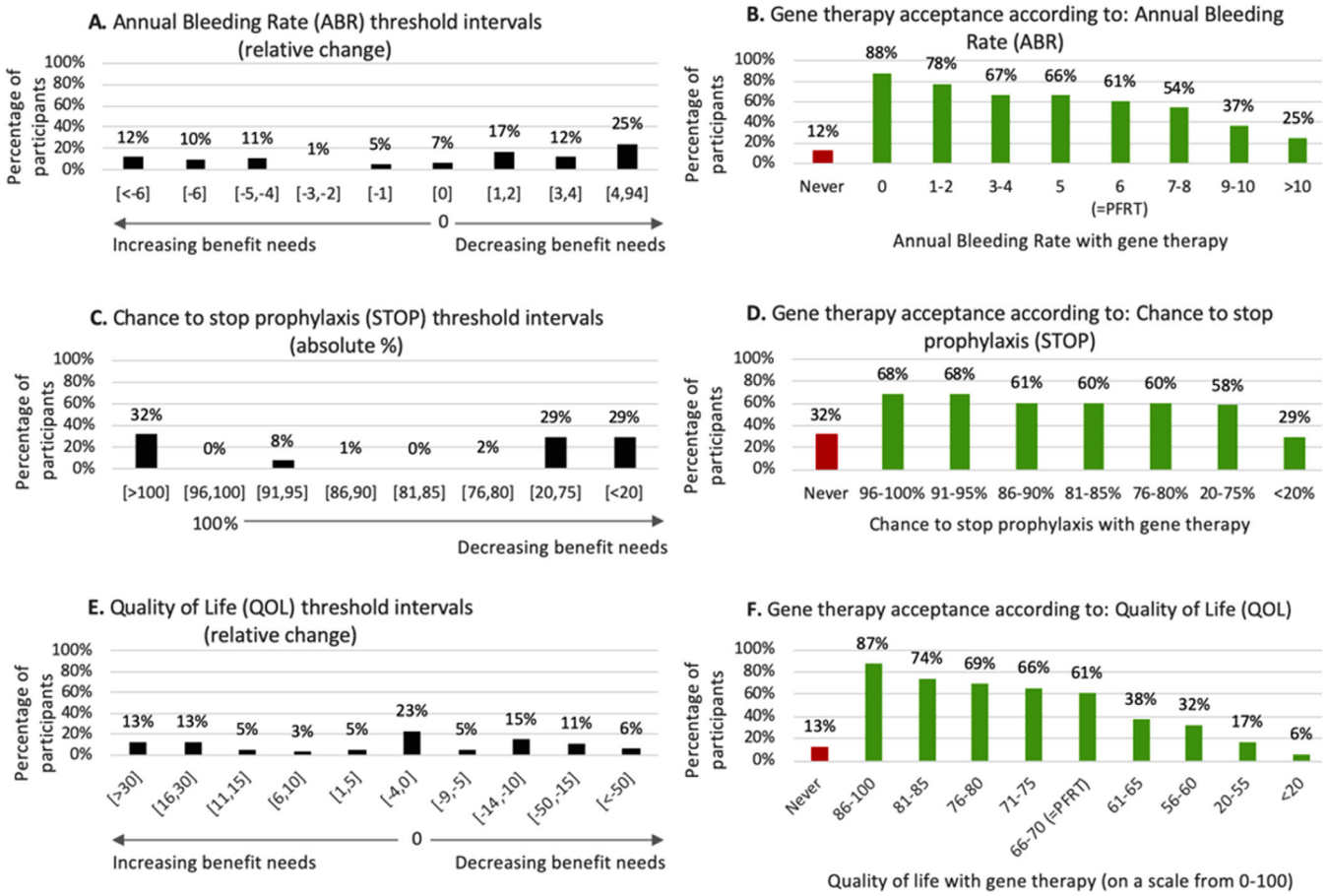

FIGURE 3 Percentage of participants per threshold interval for the attributes and total gene therapy acceptance per attribute level. Annual Bleeding Rate (ABR): (A). threshold intervals, (B). acceptance; Chance to stop prophylaxis (STOP): (C). threshold intervals, (D). acceptance; Quality of Life (QOL): (E). threshold intervals, (F). acceptance. Threshold intervals represent participants' relative minimum acceptable benefit (MAB) to be gained from gene therapy compared to prophylactic factor replacement therapy (PFRT). Intervals (A, C, E) from left to right entail decreasing benefit needs to accept gene therapy. Therefore, participants that fall within intervals on the right side of these graphs more easily accept gene therapy than those on the left. Gene therapy acceptance (B, D, F) was calculated based on the percentage of participants for whom the difference between absolute gene therapy and PFRT levels equals or surpasses their threshold. Gene therapy acceptance is shown using absolute levels included in the survey and the percentage of participants that would accept gene therapy at that level

these non-switchers commented that they believed gene therapy to be too uncertain, that it could provide more benefit to younger PWH, and that it could not reverse the damage that haemophilia had already done. Two other participants also commented that the TIME attribute was very important and that their answers would have been different if the levels of this attribute would have varied.

3.4 | Survey evaluation

In the final part of the survey, participants were asked several questions to evaluate survey performance. The QOL attribute was interpreted similarly by participants, labelling a QoL score of 70 as 'good' (60%), or as 'acceptable' (30%). Most participants found the threshold questions 'easy' or even 'very easy' to understand (67%) and to answer to (65%) and found that the educational tool helped 'very much' (49%) or 'moderately' (27%). The median time spent on the educational tool was 12.5 min, likely meaning that at least half of participants completed the full tool (minimum necessary time = 10 min). The length of the survey was mostly found to be 'just right' (28%) or 'manageable' (60%). While it seemed that some participants took over 60 minu to complete the survey, the reported duration did not take breaks into account.

4 | DISCUSSION

In this study, preferences of PWH were investigated regarding a novel promising but uncertain therapy, namely gene therapy, and a well-known standard of care (PFRT) to reveal the MAB needed to switch from PFRT to gene therapy. Moreover, preference heterogeneity was identified. HTA representatives have shown interest in the exploration of preference heterogeneity as they find it to be inevitable and inherent.[19,20] This study also revealed the benefit thresholds at which most PWH would accept gene therapy. The most accepted (88%) gene

TABLE 2 Results from the benefit threshold interval regression models

Benefit assessed in the model	ABR			STOP			QOL		
Switch (with relative change in attributes induced by the switch)	PFRT to GT (+90 STOP, -20 TIME, +0 QOL)			PFRT to GT (+0 ABR, -20 TIME, +0 QOL)			PFRT to GT (+0 ABR, +90 STOP, -20 TIME)		
Sample (n)	117			117			117		
Covariate[a]	Coef.	SE	p-value	Coef.	SE	p-value	Coef.	SE	p-value
Age	-.127	.073	.084	1.209	.477	.011	.179	.151	.235
Type of haemophilia	-.839	3.029	.782	-26.041	19.986	.193	-5.444	6.232	.382
Severity of haemophilia	-.225	2.947	.939	4.212	19.208	.826	-1.487	6.115	.808
Annual Bleeding Rate	.090	.044	.041	.476	.281	.091	.168	.093	.071
Recruitment source[b]									
°*Patient organization*	-3.153	3.453	.361	5.540	22.420	.805	4.689	7.121	.510
°*Pre-test sample*	-1.503	3.800	.693	-11.079	24.673	.653	-1.157	7.775	.882
Region of residence[c]									
°*Brussels*	-3.805	3.680	.301	44.132	23.527	.061	14.782	7.724	.056
°*Wallonia*	-4.938	2.524	.050	54.901	17.295	.002	14.323	5.211	.006
Time on educational tool	.045	.015	.003	-.323	.178	.070	-.118	.055	.031
Response to comprehension question	5.590	4.144	.177	-96.957	32.678	.003	-9.870	8.540	.248
Choice consistency	3.637	5.506	.509	6.027	32.940	.855	12.052	11.412	.291
Constant	-.299	8.649	.972	92.065	55.682	.098	-9.721	17.845	.586
Log likelihood	-406.005			-295.886			-363.176		
LR chi^2	19.64			32.06			23.68		
p-value (chi^2)	.051			.001			.014		

[a]For more information on selection and definition of covariates, please see the Supporting Information.
[b]Base: Haemophilia reference centre (*source_hrc*).
[c]Base: Flanders (*residence_flanders*).

therapy profile proved to be zero bleeds per year (vs. six for PFRT), 90% chance to stop prophylaxis, no impact on QoL, and 10 years of follow-up on side effects (vs. 30 for PFRT). Moreover, 8% of PWH seemed to never accept gene therapy under the presented conditions.

4.1 | Sources of preference heterogeneity

From the covariate-adjusted interval regression models, some characteristics of PWH were identified to influence their preferences. PWH's own ABR was found to be a predictor for their ABR threshold. PWH with higher ABRs may be used to managing bleeds and tolerate higher additional numbers of bleeds, as we suspect the importance to PWH of a change from 13 to 16 bleeds to be less significant than from 3 to 6 bleeds, for example. Furthermore, a correlation between ABR and treatment satisfaction was observed, indicating that PWH with higher ABR may be less satisfied with their current treatment and more inclined to accept gene therapy.

Older PWH and those who responded incorrectly to the comprehension question required higher chance to stop prophylaxis (STOP), to accept gene therapy. Adequate health literacy was positively correlated with correct comprehension and excluded from the model. PWH with inadequate health literacy may thus not have well-understood questions in which STOP was varied. Regarding the effect of age on the STOP threshold, in the interviews a PWH mentioned that STOP would become more important as he would get older due to potential complications that hamper self-administration of PFRT and loss of autonomy.[27] The number of damaged joints was positively correlated with age, potentially contributing to this fear of loss of autonomy.

The educational tool supported participants effectively in understanding the threshold questions. Moreover, the more time participants spent on the tool, the less ABR and QOL benefit they required to switch to gene therapy. As self-reported limited knowledge on gene therapy was found to be correlated with time spent on the educational tool, the tool seemed to have mainly helped participants with limited prior knowledge and to have resulted in patient activation.[31] Educational tools have also been found to play a crucial role in measuring consumer preferences for new products.[32,33]

A significant effect of residence (mainly Flanders vs. Wallonia) on all benefit thresholds was observed. A correlation was observed between residence and prior discussion on gene therapy with a clinician as proportionally more PWH in Wallonia had discussed gene therapy with their clinician. It remains uncertain why these PWH had higher thresholds for all benefits than PWH in Flanders. The effect of residence on MAB thresholds may be explained by differences in culture, lifestyle, education and healthcare.[34–38]

4.2 | Strengths and limitations

Our study adhered to the five considerations of van Overbeeke et al.[20] to ensure value of patient preference studies for decision making. Moreover, it also met quality indicators of the FDA.[39,40] Strengths and limitations relating to the study design have been described. We hypothesized that both attributes ABR and QOL could be included in the survey as PWH with the same QOL could have different ABR and vice versa, and this was proven by the results of this survey.[25]

Based on the sample characteristics and population data, we believe that our sample was representative to the Belgian PWH population eligible for gene therapy treatment. Often, patient preference studies have limitations relating to recruitment through panels and patient organizations, and self-reported diagnosis.[41,42] This was not the case for our study as 80% of our sample was confirmed as PWH and invited by a haematologist through a haemophilia reference centres. Moreover, PWH A and B were represented according to their prevalence, PWH A and severe PWH had higher PFRT administration frequencies as expected, and PWH of different regions, ages, employment statuses, health literacy and quality of life participated. While female haemophilia patients are very rare, 1% of our sample was female which is in line with population estimations based on data provided by the patient organization (0%–1,97%). Contributing to our representativeness claims are the noteworthy participation rates. We reached a participation rate of 40% in haemophilia reference centres and an eligible population participation rate of 26% (n = 117, N = 449). While not all participants received PFRT, we are confident that participants understood the benefits and risks of PFRT (facilitated by current clinical care and the educational tool), and that this did not affect our results.

While defining the TIME attribute, relating to uncertainty regarding long term risks, as the 'time that side effects have been studied' in years total facilitated comprehension by participants, we acknowledge that the use of patient years could have more accurately reflected the extent of data available on PFRT and gene therapy. Our study only investigated PWH's needs for a switch from PFRT to gene therapy and did not address other haemophilia treatments such as non-factor replacement therapies (e.g., emicizumab). This study was conducted during the COVID-19 pandemic and it is unclear what the effect of this outbreak was on PWH's preferences. As the pandemic may have long-term implications on healthcare and life, we believe a study conducted during this pandemic is more representative of future perspectives than a study conducted prior to the outbreak.

Throughout the survey, internal validity checks were incorporated. Only one respondent failed two or more of these tests and this respondent was excluded from the analysis. A limited number of respondents failed one validity check. We believe that most PWH made informed choices as only 23 participants (19.7%) spent less than 7 min on the educational tool and most patients had already discussed gene therapy treatment with their clinician.

4.3 | Future perspectives

The innovative character of gene therapy may play a role in its acceptance and over time that acceptance may increase according to Roger's Diffusion of Innovation Theory.[43] While we were not able to investigate TIME thresholds, participants indicated that their preferences would change with varying levels of uncertainty regarding long-term risks. Moreover, in the interviews uncertainty regarding long-term risks was identified as one of the top attributes important to PWH.[27] Therefore, future research should focus on quantifying the impact of uncertainties and other potential risks on gene therapy preferences of PWH. Moreover, future research could investigate preferences of PWH when comparing emicizumab to gene therapy.

4.4 | Impact on decision making

The results of this study may inform HTA and payer decision-making, as well as regulatory and shared decision-making, as confirmed in a final advisory board of the PAVING study in April 2021, that included HTA, payer, industry and clinical representatives. The education tool developed for this study could be transformed into a decision aid to further guide PWH and clinicians in shared decision-making on individual treatment. The results could inform weighing and acceptability of risks, benefits and uncertainties, and valuation of new decision-making elements that go beyond health gain.[15–17,44] Value-based pricing and budget impact analysis of gene therapies could be informed by the identified MABs and subgroups that may never accept these therapies; reducing the expected budget impact.[44] If the TIME attribute would be investigated in a future preference study, it may be possible to model the evolution of expected uptake over time. If distribution of uptake over time would be likely to occur, this could entail that budget impact peaks at launch of gene therapies may be lower than is currently expected.

5 | CONCLUSIONS

Preferences for gene therapy in haemophilia are remarkably heterogenous. To switch from PFRT to gene therapy, some PWH required less benefit than was initially offered, while others required more or would even never accept gene therapy under the conditions presented in the survey. This heterogeneity could be explained by characteristics such as PWH's own ABR, age, comprehension, and especially by the time spent on the educational tool and residence (Flanders vs. Wallonia). The educational tool included in this study educated PWH effectively, and even led to increased acceptance. Educational tools and methods that can explore preference heterogeneity in-depth play an important role in eliciting patient preferences for innovative treatments. We hope that the results from the PAVING study can help inform HTA, payer, regulatory and shared decision-making on gene therapies, and that our results drive these stakeholders to consider preference heterogene-

ity and the impact of patient education on gene therapy acceptance in their decisions.

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CONSENT TO PARTICIPATE

All patients provided electronic informed consent prior to their participation.

CONSENT TO PUBLISH

All provided electronic informed consent for the use of the collected data for publication.

CONFLICT OF INTEREST

The authors have no competing interests to declare. While Eline van Overbeeke and Brett Hauber are currently employed by Pfizer, they were employed by the University of Leuven and RTI Health Solutions, respectively, when the study was designed and conducted.

AUTHOR CONTRIBUTIONS

Eline van Overbeeke, Brett Hauber, Sissel Michelsen, Kathelijne Peerlinck, Catherine Lambert, Cedric Hermans, Michel Goldman, Steven Simoens, Isabelle Huys were involved in the design of the study. Eline van Overbeeke facilitated recruitment through interaction with clinicians Kathelijne Peerlinck, Catherine Lambert, Cedric Hermans and Phu Quoc Lê, and performed the analysis of results in consultation with Brett Hauber and Isabelle Huys. Eline van Overbeeke produced the first draft of the manuscript, which was subsequently revised and finalized with all authors. All authors approved the final manuscript.

DATA AVAILABILITY STATEMENT

Data are available upon request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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