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Gene-Targeted Therapies Working Group:

Patient preference studies for gene-targeted therapy

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Massachusetts General Hospital

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REiNS

Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

Goals of working group

- To discuss ethical issues surrounding trials of gene therapy with all stakeholders
- To propose clinical trial endpoints for gene therapy that can lead to drug approvals for NF1 and SWN

Members of working group

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Would you consider gene therapy for the following NF1 clinical scenarios?

For treatment of:

- Prevention of MPNST conversion
- Inoperable and progressive plexiform (with or without selumetinib)
- Symptomatic optic pathway glioma, progressive. Treated or not treated?
- Severe cognitive impairment at early age (4 years) - falls behind peers, not meeting milestones
- Tibial pseudarthrosis at young age
- Cutaneous neurofibromas – can consider young person at risk for many or older person with heavy tumor burden
- Early cNF, 1 plexiform, and cognitive/social deficit – age 9
- Young child with *NF1* gene microdeletion
- stable pNF – symptomatic inoperable (slow growing)
- OPG – progressive vs. stable lesions. With vision loss, without?

Would you consider gene therapy for the following SWN clinical scenarios?

Treatment of:

- 12 year old person with severe genetic severity score and a few small tumors.
- 35 year old with worsening hearing loss and vestibular schwannomas that are no longer responding to bevacizumab (but no other tumors).
- 44 year old with deafness and heavy burden of spinal tumors and who is now wheel chair bound.
- 50 year old with intractable pain despite multiple medications and spinal cord stimulator.

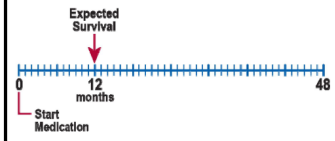
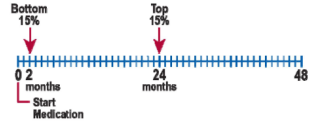
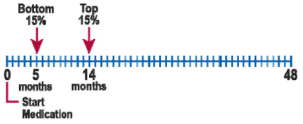
Importance of patient engagement

- FDA and EMA increasingly recognizing "*the added value of patients in benefit-risk considerations*"
- EMA: "*an excessive focus on avoiding risks and uncertainties concerning new medicines might be against the interests of patients, delaying or reducing access to potentially life-saving treatments*'"
- Patients and families with rare diseases (and diseases without treatments) have urged regulators to be more permissive and to allow for drugs with greater risk or side effects than traditionally accepted
- Gene targeted therapy is a new field of medicine with uncertain risks and benefits. It holds great promise for patients with genetic tumor suppressor syndromes.

EMA, Roadmap to 2015, 2010
EMA, Workshop, 2014
Morel et al., Orphanet Journal of Rare Diseases, 2016

Discrete choice exercises (DCEs) can explore the relative importance of the benefits and risks of different treatments to patients and clinicians

- Treatments are composed of a set of features, or 'attributes' (i.e., risks and benefits)
- The relative value of a particular treatment to an individual is a function of these attributes
- Example of cancer studies: To quantify the extent to which patients and clinicians weigh survival benefits against treatment-related side effecdts

Treatment Feature	Treatment A	Treatment B
Expected survival with treatment		
Survival for bottom 15% of patients Survival for top 15% of patients		
Fatigue	No fatigue	Mild to moderate fatigue (Grades 1 and 2)
Nausea	Mild to moderate nausea (Grades 1 and 2)	No nausea
Risk of febrile neutropenia	 10% (2 out of 20)	 40% (8 out of 20)
Which would you choose	☐	☐

Physician version

Hauber et al., Patient preference experience, 2020

First step in DCE is to identify treatment attributes for consideration

In the table below, please indicate the six elements that you think are most important when deciding whether gene therapy is the right treatment for you/your child (using scores from 1 to 6, with "1" being the most important element).

Categories	***Elements***	*Definition*	***Ranking***
Follow-up	**Frequency of monitoring**	The number of times a patient has to visit a physician for follow-up on the effect of the treatment within a specific time period (e.g. once per month, once per year)	
Benefits	**Effect on factor level**	The effect on the amount of working clotting factor in the blood, delivered via factor replacement therapy or produced by the patient after gene therapy (often expressed in percentage, %, of normal levels)	
	Effect on annual bleeding rate	The effect of the treatment on the number of bleeding events per year	
	Probability that prophylaxis can be stopped after treatment	The chance that use of prophylactic factor replacement therapy can be stopped after treatment (expressed in percentage, %, of patients that can stop prophylaxis)	
	Uncertainty regarding long-term benefits	The degree of uncertainty that the effect of the treatment will be maintained after administration of the treatment (uncertainty may exist because of limited time that patients were followed-up after treatment administration, or because of limited numbers of patients treated with the treatment)	
Quality of Life	**Impact on daily life**	The impact of the treatment on daily activities	
	Impact on participation in physical activity	The impact of the treatment on the performance of physical activity (sports)	
	Possibility to undergo major surgery	The impact of the treatment on the possibility to undergo major surgery	
Risks	**Probability that liver inflammation will develop**	The chance that liver inflammation develops after treatment (expressed in percentage, %, of patients that develops liver inflammation)	
	Uncertainty regarding long-term risks	The degree of uncertainty regarding the side effects that can occur after administration of the treatment (uncertainty may exist because of limited time that patients were followed-up after treatment administration, or because of limited numbers of patients treated with the treatment)	

TABLE 2 Top 10 attributes important to patients.

Rank	Attribute	Score*
1	Effect on annual bleeding rate	47
2	Factor level	43
3	Uncertainty long-term risks	39
4	Impact on daily life	39
5	Probability that prophylaxis can be stopped	32
6	Possibility of undergoing major surgery	26
7	Route of administration	21
8	Probability of liver inflammation	21
9	Mechanism of action	20
10	Dose frequency	17

*n = 18; maximum score is 108 (6 points x 18 interviewees) per attribute.

Van Overbeeke et al. (2020) Patient perspectives regarding gene therapy in haemophilia: Interviews from the PAVING study.

Using treatment attributes to create a discrete choice exercise for hemophilia

Treatment Attributes

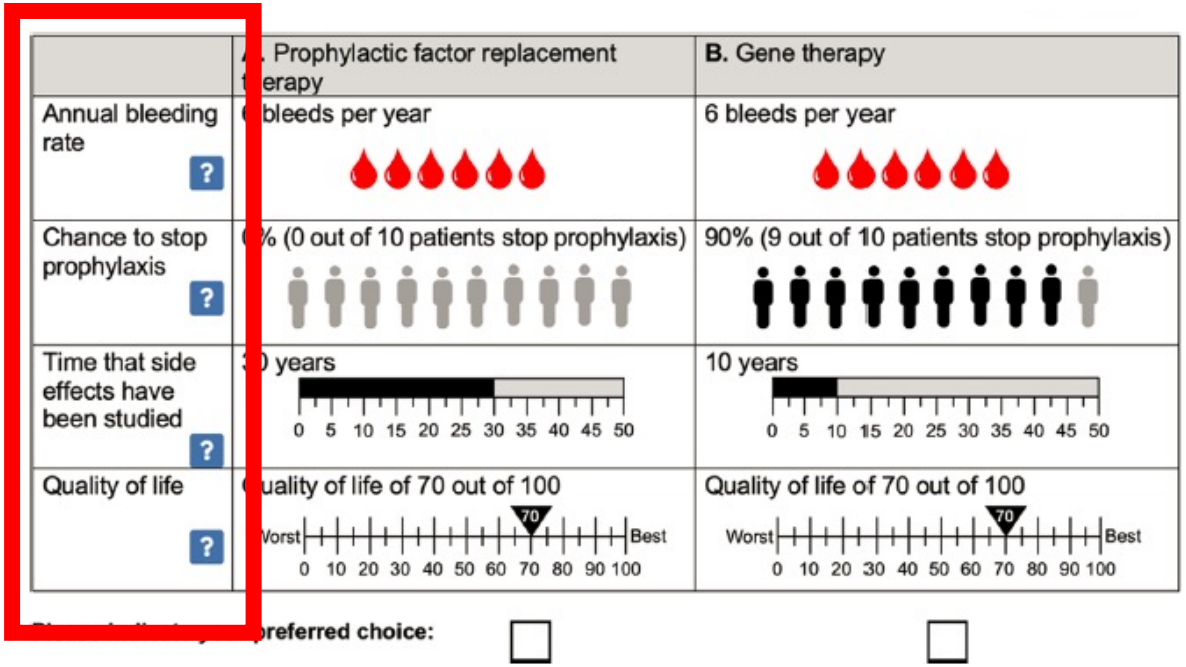
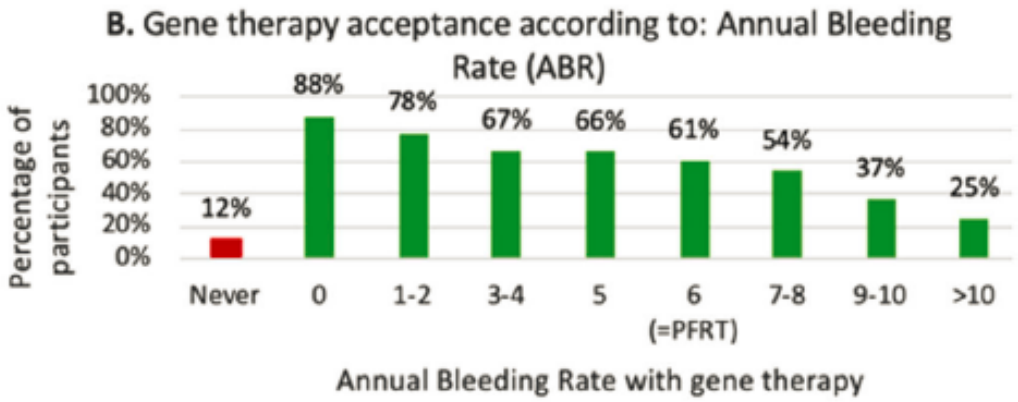


FIGURE 1 First threshold technique question showing the baseline attribute levels included in the survey

Van Overbeeke et al. (2021) Patient preferences for gene therapy in haemophilia: Results from the PAVING threshold technique survey.

Hemophilia: Balancing bleeding risk, impact on quality of life, and long term safety



On average, participants would accept an additional 1.3 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.

On average, participants required 65% 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

Challenges of preference studies in NF1 and SWN

- Germline genetic variants cause NF1 and SWN
- However, disease manifestations vary widely among families and individuals
- How to create discrete choice exercises for NF1 and SWN when gene-targeted therapies may have specific and general effects?

Next steps

- Initial exercise to understand patient and clinician preference was completed in June, 2022
- Next steps will be to refine treatment attributes and create a discrete choice exercise

- To join gene-targeted therapy group, email splotkin@mgh.Harvard.edu

- Thanks to Gin-Nie Chua and Vanessa Merker
- Thanks to Dani Silverman

Patient preference studies can help understand preference for gene therapy in genetic conditions like hemophilia

	A. Prophylactic factor replacement therapy	B. Gene therapy
Annual bleeding rate	6 bleeds per year	6 bleeds per year
Chance to stop prophylaxis	0% (0 out of 10 patients stop prophylaxis)	90% (9 out of 10 patients stop prophylaxis)
Time that side effects have been studied	30 years 0 5 10 15 20 25 30 35 40 45 50	10 years 0 5 10 15 20 25 30 35 40 45 50
Quality of life	Quality of life of 70 out of 100 Worst 70 Best 0 10 20 30 40 50 60 70 80 90 100	Quality of life of 70 out of 100 Worst 70 Best 0 10 20 30 40 50 60 70 80 90 100

Please indicate your preferred choice: ☐ ☐

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

Van Overbeeke et al. (2021) Patient preferences for gene therapy in haemophilia: Results from the PAVING threshold technique survey.