

The Value Generation-Recognition Gap for Novel Gene Therapies in European HTA Systems using X-linked Retinitis Pigmentosa as a Case Study



Jennifer Lee¹, Jake Hitch², Simon Brassel², Jacob Petersen¹, Tom Denee³, Martina Garau², Lotte Steuten²

¹Janssen EMEA, Copenhagen, Denmark, ²Office of Health Economics, London, UK, ³Janssen EMEA, Breda, Netherlands

Contact: Simon Brassel, sbrassel@ohe.org

RATIONALE AND BACKGROUND ON XLRP

- Gene therapies challenge the status quo in value assessment because they potentially generate broader value than typically considered by HTA agencies e.g. improved educational and employment opportunities, as well as lifetime productivity gains [1].
- Many of these broader value elements are not considered by most HTA agencies partly because of methodological challenges, lack of data and/or lack of political will [4].
- Although several studies have been published on the HTA of cell and gene therapies [3-5], more research is needed to understand the value of gene therapies for inherited retinal dystrophies (IRDs) – a group of diseases that can cause severe vision loss or even blindness.
- More specifically, no study has attempted to identify the potential value generation-recognition gap for gene therapies that can halt and/or intercept further progression of XLRP – a rare type of IRD that causes progressive vision loss, predominantly in males - or other progressive IRDs.

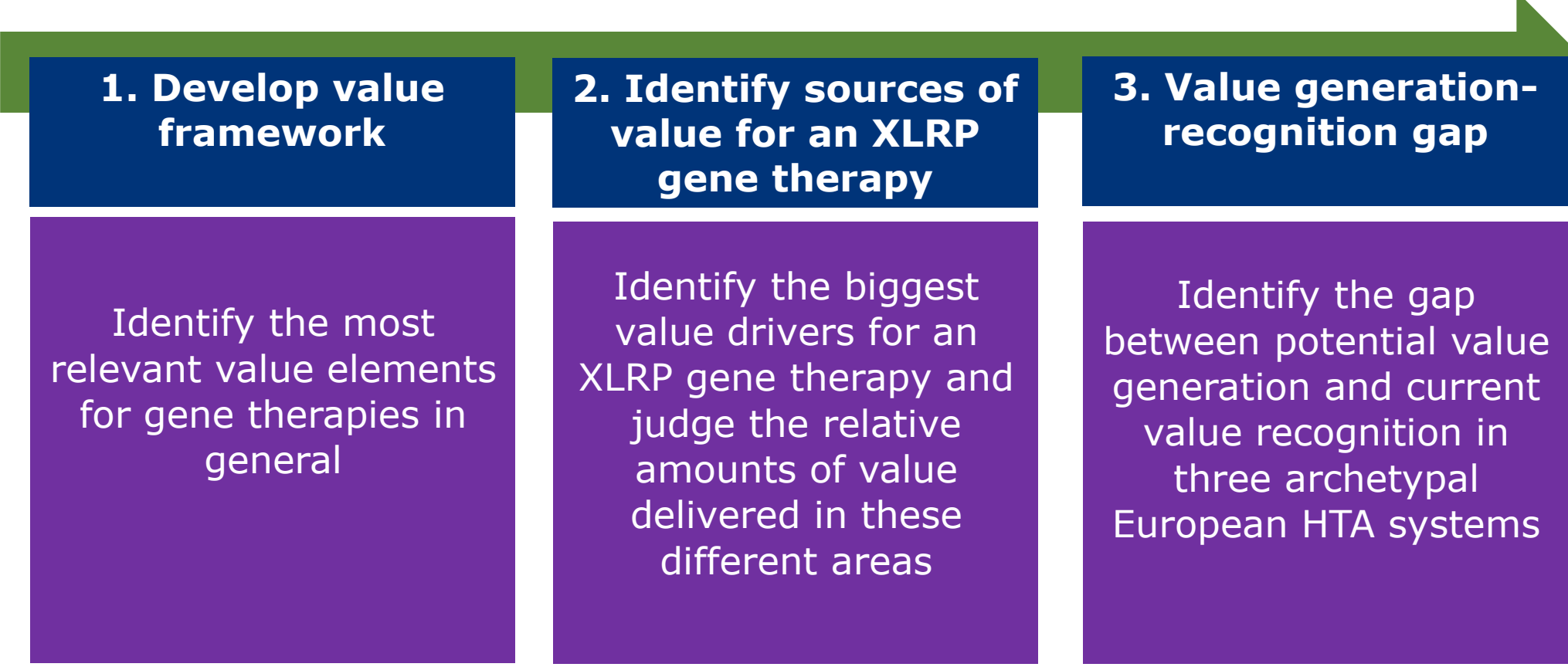
OBJECTIVE

To identify the gap between potential value generation and current value recognition for a future gene therapy targeting XLRP from an HTA perspective.

METHODS

An overview of the methods used is presented in **Figure 1**.

Figure 1. Overview of methods: main steps and aims



1. Gene therapies value framework

- Aim: to identify the most relevant value elements for gene therapies.
- We began with the version of the widely-cited value flower presented by Neumann et al. (2022) [6].
- We then reviewed the relevant literature on value assessment of gene therapies [3-5], to identify additional relevant value elements and remove less relevant ones.
 - This included searches of PubMed and Google Scholar, and forward and backward snowballing of key references from these searches.

2. Value generated by an XLRP gene therapy

- Aim: to identify the relevance of each value element for XLRP and therefore the main sources of value delivered by an effective XLRP gene therapy.
- We conducted a targeted search of the peer-reviewed and grey literature on XLRP and similar retinal diseases to identify the main costs and effects associated with the disease [e.g. 7-11].
- We used diamond icons to represent the importance of each value element as a value driver i.e. how much value comes from each source compared to the total value delivered by the gene therapy product:

Value generation-recognition gap

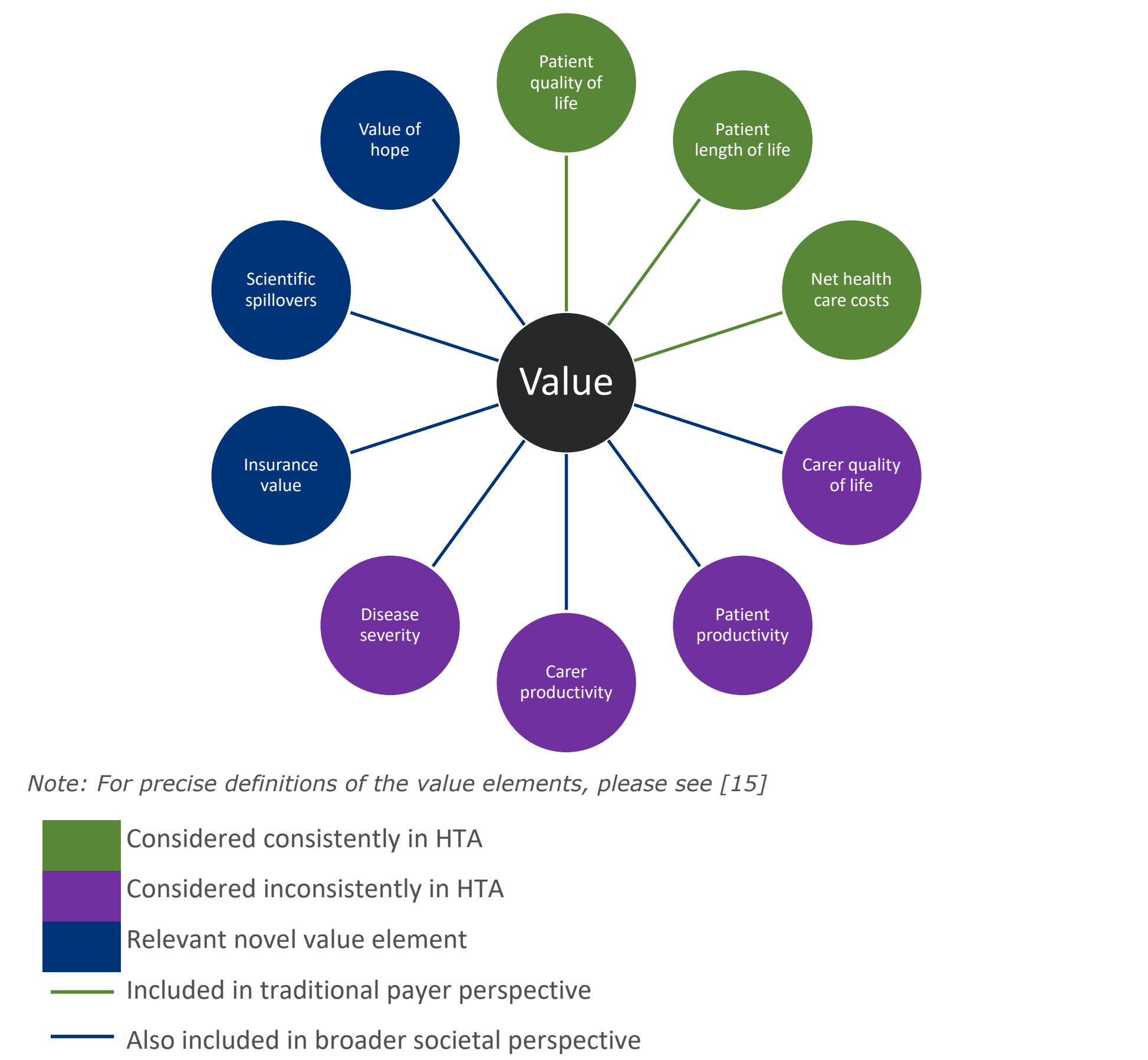
- Aim: to compare this potential value generation to current value recognition in three European HTA systems.
- We reviewed HTA methods documents published by NICE (England) [12], ZIN (Netherlands) [13] and HAS (France) [14], and relevant past technology appraisals, mainly voretigene neparovvec [3].
- For each value element we identified:
 - whether the guidelines recommend including the value element in the reference/base case economic evaluation or sensitivity analysis.
 - whether the guidelines state that the value element will be considered deliberately in HTA.
 - whether the value element was considered in the evaluation of voretigene neparovvec.
- We chose these three countries as they are three large European HTA systems and represent a variety of perspectives and approaches to HTA.

RESULTS & DISCUSSION

- We identified 10 value elements of particular relevance for gene therapies (see figure 2); however, we note that this list may not be exhaustive.
- Other value considerations that are not included in figure 2 but which may be relevant in certain cases include unmet need, value of equity, fear of disease, and losses in tax revenue due to reduced workforce participation.
- However, the 10 value elements included here are likely to be meaningful sources of value for the archetypal gene therapy without significant overlap between any elements that could create the problem of double counting.
- All elements but net health care costs are likely to deliver positive value in the case of XLRP (see table 2). This is because most of the costs currently borne by these patients are incurred in the social and welfare sector, as opposed to the direct healthcare sector.

- Compared to the standard value flower [6], we separated QALYs into patients' quality and length of life to better capture the value profile of a gene therapy for XLRP. For the same reason we also separated "family spillovers" into carer quality of life and carer productivity (see figure 2).
- Value of knowing was removed because this element is relevant mainly for diagnostics, not treatments [15]. Fear of contagion was removed because to date, no gene therapy has been assessed for an infectious disease [4].

Figure 2. Value flower for gene therapies



- Table 1 lists the value elements relevant for gene therapies and describes the relevance of each for XLRP. The colour coding is the same as for figure 2.

Table 1. Gene therapy value flower elements and detail on relevance for XLRP

	Value element	Relevance for XLRP
Considered consistently in HTA	Patient quality of life	The health-related quality of life (HRQoL) of people living with IRDs has been estimated to be significantly lower than population norms (0.58 vs. 0.8) [18]. XLRP affects quality of life through various channels including the patient's ability to carry out normal activities, psychosocial burden, and educational and work opportunities [8]. Impacts on patients' wellbeing account for 37.5% of the total costs associated with IRDs in the UK [7].
	Patient length of life	The main symptoms of XLRP are visual impairment and blindness; IRDs do not have a direct impact on mortality risk [3]. However, retinitis pigmentosa (RP) may lead to additional mortality indirectly through suicide [11] and possibly through increased risk of injuries [19]. Nevertheless, the main impact will be on quality rather than length of life.
	Net health care costs	The upfront costs of a one-off XLRP gene therapy are likely to be relatively high. This will have to be weighed against some likely cost savings [10]. However, due to the lack of longer-term evidence on healthcare use, the impact on long-term health service costs is unclear.
Considered inconsistently in HTA	Carer quality of life	Taking on caring responsibilities is likely to have a negative impact on quality of life, particularly when the patient is a child or adolescent. 78% of parents/guardians of children living with an IRD report suffering from anxiety and the same percentage report depression [7]. At later disease stages, often when patients are 20-30 years old, patients are not allowed to drive and will require support to move around. Patients subsequently develop severe blindness, requiring support to complete daily activities.
	Patient productivity	Productivity costs have been estimated to account for 22% and 19% of total costs associated with IRDs in the UK and Republic of Ireland respectively [7]. Childhood-onset retinal dystrophies may reduce lifetime income by 30%, and this is likely to be explained partly by educational impacts [9]. Qualitative evidence suggests XLRP creates barriers to work and education, both of which affect earnings [8].
	Carer productivity	As well as the quality of life impact, informal carers will have to take time away from paid employment. Informal carer costs have been estimated to account for 16% and 14% of total costs associated with IRDs in the UK and Republic of Ireland [7].
	Disease severity	XLRP is a severe disease in terms of impact on patient quality of life. However, the QALY shortfall for XLRP patients is uncertain and this is how NICE and ZIN measure severity. The proportional QALY shortfall of RPE-65 IRDs has been estimated to be 69% [3] and this may potentially be indicative for XLRP.
Potential novel value element	Insurance value	Insurance value comes from financial risk protection and physical risk protection [15]. Physical risk protection is more relevant for European health systems and refers to the fact that an effective treatment for XLRP would insure diagnosed and potential XLRP patients against uncertain poor health states in the future. Given the genetic nature of the disease, parents may also derive insurance value from the existence of an effective treatment that will ensure their children against severe vision loss.
	Scientific spillovers	Scientific spillovers have been identified as a key consideration for gene therapies [1] but are notoriously hard to quantify. However, given that gene therapies are still a nascent technology and no effective treatments exist for XLRP, it is likely that the development of an XLRP gene therapy will generate some scientific knowledge, skills, and experience that may facilitate the development of treatments for retinal and other diseases in the future.
	Value of hope	With many gene therapies, there is a chance of transformative health benefits for the patient [16]. While it is currently impossible to accurately quantify the amount of value of hope that an XLRP could deliver, if there is any chance of halting or significantly decelerating vision loss for some patients (which evidence suggests it will [17]), then it will deliver some value of hope, at least for certain groups of patients and their families and carers.

Table 2. Value generation-recognition gap for a gene therapy for XLRP

Country	Patient quality of life	Patient length of life ¹	Net health care costs ²	Carer quality of life	Patient productivity	Carer productivity	Disease severity ³	Insurance value	Scientific spillovers	Value of hope ⁴

Note: ¹XLRP has a limited impact on life expectancy (see table 1), ²Uncertainty about pricing and long-term health service use by XLRP patients makes the impact on net costs too uncertain to assess its importance as a value driver/detractor, ³The severity modifiers used by NICE and ZIN are both based partly on proportional QALY shortfall (PS) but there are no estimates of the PS for XLRP patients so it is unclear how the severity of XLRP would be operationalised if at all

- Recommended for reference/base case economic evaluation
 - Recommended for sensitivity analysis
 - Not recommended in economic evaluation but could potentially be considered deliberately
- The number of diamonds indicates the importance of each element as a value driver for an XLRP gene therapy. One, two, and three diamonds represent limited, moderate, and significant value drivers respectively.

- An XLRP gene therapy may potentially deliver value on 8 of the 10 value elements identified to be particularly relevant for valuing gene therapies in general (patient quality of life, carer quality of life, patient productivity, carer productivity, disease severity, scientific spillovers and insurance value).
- Currently, the full value of an XLRP gene therapy is unlikely to be captured in HTA in the three countries under study:
 - HTA agencies across Europe are unlikely to consistently capture the full value of patient and carer productivity effects, apart from those taking a societal perspective such as the Netherlands. Although these effects can and have been incorporated quantitatively into HTA in the past, whether or not they are actually included is likely to be decided at a political level.
 - Insurance value, scientific spillovers, and the value of hope are likely sources of value for an XLRP gene therapy. However, they have rarely, if ever, been considered in health technology assessments [6,15]. This is partly because it is challenging to estimate the order of magnitude of those but may also be due to a lack of political will.

CONCLUSIONS

- There is likely to be a meaningful value generation-recognition gap for XLRP gene therapies in three leading European HTA systems.
- The biggest contributors to this gap are likely to be insurance value and disease severity, as well as patient productivity effects and carer spillovers. The novel value elements hope value and scientific spillovers also contribute to this gap.
- Undervaluation of gene therapies for progressive IRDs could have detrimental health and societal effects due to delayed or limited patient access.
- To avoid this undervaluation, HTA agencies should update the value frameworks they use for the assessment of gene therapies and work to address methodological and data challenges that are limiting the consideration of significant value drivers.

REFERENCES

- Drummond, Michael F., Peter J. Neumann, Sean D. Sullivan, Frank-Ulrich Fricke, Sean Tunis, Omar Dabbous, and Mondher Toumi. "Analytic Considerations in Applying a General Economic Evaluation Reference Case to Gene Therapy". *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research* 22, no. 6 (June 2019): 661-68.
- Tsang, Stephen H., and Tarun Sharma (eds.). "X-Linked Retinitis Pigmentosa". In *Atlas of Inherited Retinal Diseases*, 1st ed., 31-35. *Advances in Experimental Medicine and Biology*. Springer Cham, 2018.
- Huygens, Simone A., Matthijs M. Versteegh, Stefan Vegter, J. Jan Schouten, and Tim A. Kanter. "Methodological Challenges in the Economic Evaluation of a Gene Therapy for RPE65-Mediated Inherited Retinal Disease: The Value of Vision". *Pharmacoeconomics* 39, no. 4 (April 2021): 383-97.
- Besley, Sian, Nadine Henderson, Adrian Towse, and Amanda Cole. "Health Technology Assessment of Gene Therapies: Are Our Methods Fit for Purpose?" OHE Consulting Report. London: Office of Health Economics, 30 June 2022.
- Pinho-Gomes, Ana-Catarina, and John Cairns. "Evaluation of Advanced Therapy Medicinal Products by the National Institute for Health and Care Excellence (NICE): An Updated Review". *Pharmacoeconomics - Open* 6, no. 2 (March 2022): 147-67.
- Neumann, Peter J., Louis P. Garrison, and Richard J. Wilkie. "The History and Future of the 'ISPOR Value Flower': Addressing Limitations of Conventional Cost-Effectiveness Analysis". *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research* 25, no. 4 (April 2022): 558-65.
- Galvin, Orla, Gloria Chi, Laura Brady, Claire Hippert, Marta Del Valle Rubio, Avril Daly, and Michel Michaelides. "The Impact of Inherited Retinal Diseases in the Republic of Ireland (ROI) and the United Kingdom (UK) from a Cost-of-Illness Perspective". *Clinical Ophthalmology (Auckland, N.Z.)* 14 (2020): 707-19.
- Chivers, Marie, Nan Li, Feng Pan, Heather Wiegler, Rafal Slowik, and Jittraku Leartsakulpanitch. "The Burden of X-Linked Retinitis Pigmentosa on Patients and Society: A Narrative Literature Review". *ClinicoEconomics and Outcomes Research: CEOR* 13 (2021): 565-72.
- Kessel, Line, Jakob Kjellberg, Kamilla Nissen, Anette Rasmussen, and Morten la Cour. "Childhood-Onset Retinal Dystrophies Reduces Life-Time Income by One Third - an Individual Based Socio-Economic Analysis". *Ophthalmic Genetics* 43, no. 5 (October 2022): 629-34.
- Frick, Kevin D., M. Christopher Roebuck, Joshua I. Feldstein, Catherine A. McCarty, and Lori L. Grover. "Health Services Utilization and Cost of Retinitis Pigmentosa". *Archives of Ophthalmology* 130, no. 5 (1 May 2012): 629-34.
- Na, Kun-Ho, Hyun Jung Kim, Kyoung Hoon Kim, Seungjin Han, Patrick Kim, Hoo Jae Hann, and Hyeon Sik Ahn. "Prevalence, Age at Diagnosis, Mortality, and Cause of Death in Retinitis Pigmentosa in Korea-A Nationwide Population-Based Study". *American Journal of Ophthalmology* 176 (April 2017).
- National Institute for Health and Care Excellence. NICE health technology evaluations: the manual 2022
- Zorginstituut Nederlands. Guidelines for economic evaluations in Healthcare. 2016
- Haute Autorité de Santé. Choices in Methods for Economic Evaluation. 2020
- Lakdawalla, Darius N., Jelpe A. Doshi, Louis P. Garrison, Charles E. Phelps, Anirban Basu, and Patricia M. Danzon. "Defining Elements of Value in Health Care—A Health Economics Approach: An ISPOR Special Task Force Report [3]". *Value in Health* 21, no. 2 (1 February 2018): 131-39.
- Salzman, Rachel, Francesca Cook, Timothy Hunt, Harry L. Malech, Philip Reilly, Betsy Foss-Campbell, and David Barrett. "Addressing the Value of Gene Therapy and Enhancing Patient Access to Transformative Treatments". *Molecular Therapy* 26, no. 12 (5 December 2018): 2717-26.
- Michaelides, M et al. Ph1/2 AAV5-RPGR (Botaretagene Sparovovvec) Gene Therapy Trial in RPGR-associated X-linked Retinitis Pigmentosa (XLRP). Abstract #30071754. Presented at the 2022 American Academy of Ophthalmology Annual Meeting.
- Schofield, Deborah, Joshua Kraindler, Owen Tan, Rupendra Shrestha, Diana Jelovic, Sarah West, Alan Ma, John Grigg, and Robyn V. Jamieson. "Patient-Reported Health-Related Quality of Life in Individuals with Inherited Retinal Diseases". *Ophthalmology Science* 2, no. 1 (1 March 2022).
- Burton, Matthew J., Jacqueline Ramke, Ana Patricia Marques, Rupert R. A. Bourne, Nathan Congdon, Iain Jones, Brandon A. M. Ah Tong, et al. "The Lancet Global Health Commission on Global Eye Health: Vision beyond 2020". *The Lancet Global Health* 9, no. 4 (1 April 2021): e489-551.