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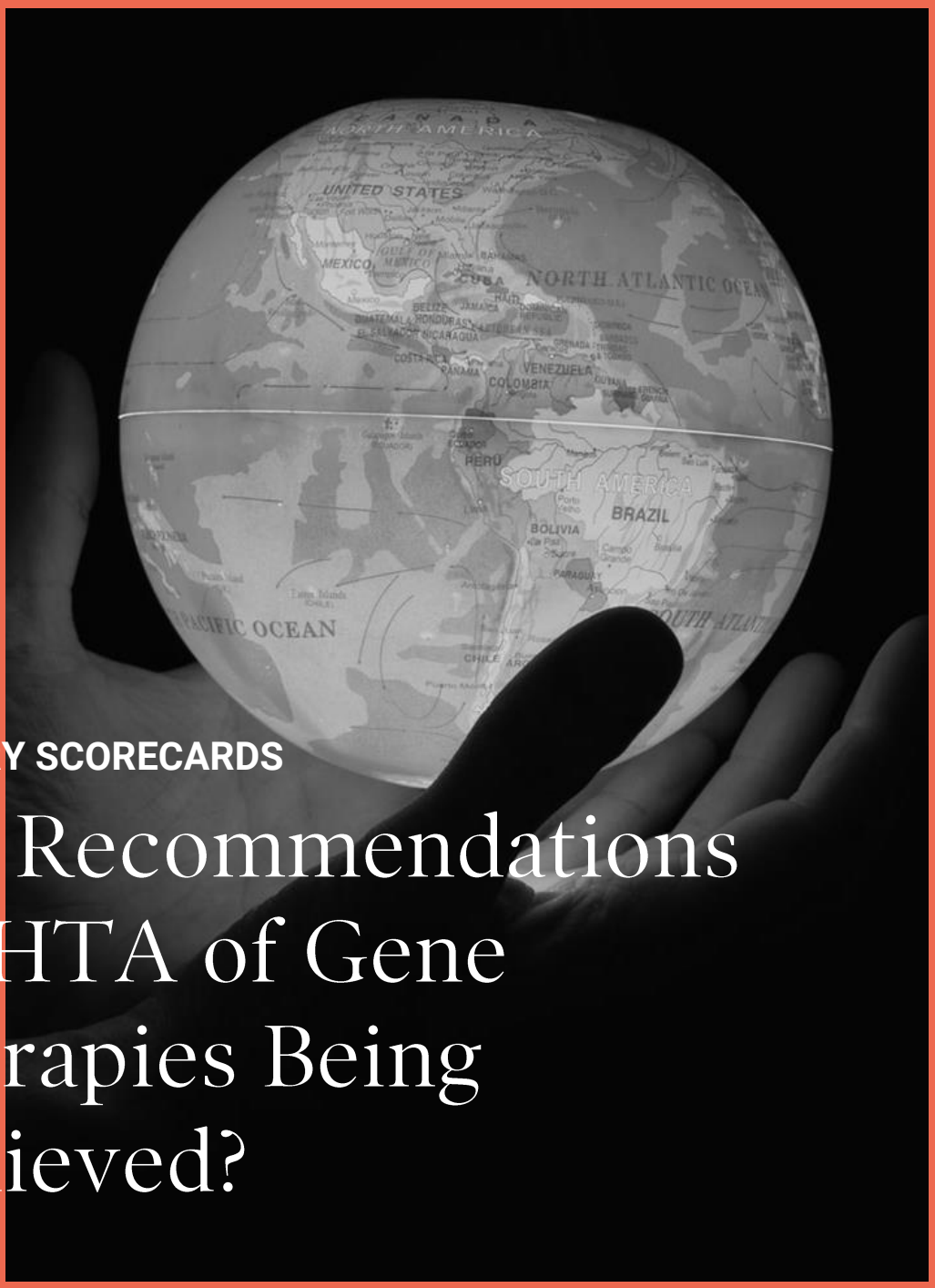

COUNTRY SCORECARDS

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CONTRACT RESEARCH REPORT
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List of abbreviations

AAZ: Croatian Agency for Quality and Accreditation in Health and Social Welfare
AbD: Anwendungsbegleitende Datenerhebung
ABDR: Australian Bleeding Disorders Registry
AEMPS: La Agencia Española de Medicamentos y Productos Sanitarios
AIFA: Agenzia Italiana del Farmaco
ALL: B-cell acute lymphoblastic leukaemia
ANMDR: Australian Neuromuscular Disease Registry
ASMR: Amélioration du Service Médical Rendu (Medicinal Added Benefit)
ATMP: Advanced Therapy Medicinal Product
BAG: Bundesamt für Gesundheit
CADTH: Canada Agency Drug and Technology Health
CDF: Cancer Drugs Fund
CED: Coverage with Evidence Development
DLBCL: Diffuse large B-cell lymphoma
DMA: Danish Medicines Agency; Laegemiddelstyrelsen
DMC: Danish Medicines Council; Medicinrådet
DNPR: Danish National Patient Registry
EBMT: European Society for Blood and Marrow Transplantation
ECFSPR: European Cystic Fibrosis Society Patient Registry
EMA: European Medicines Agency
EUnetHTA: European Network for Health Technology Assessment
FIMEA: Finnish Medicines Agency
FOPH: Federal Office for Public Health
G-BA: Gemainsamer Bundesausschuss
HAS: Haute Autorité de Santé
HST: Highly Specialised Technologies
HTA: Health Technology Assessment
ICER: Incremental Cost-Effectiveness Ratio
IMF: Innovative Medicines Fund
INFARMED: Portuguese National Authority of Medicines and Health Products
IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
JSC: Joint Scientific Consultations
MA: Medicines Australia
MSAC: Medical Services Advisory Committee
NHRA: National Health Reforms Agreement

NICE: National Institute of Health and Care Excellence

NOMA: Norwegian Medicines Agency

PBAC: Pharmaceutical Benefits Advisory Committee

PBS: Pharmaceutical Benefits Scheme

PLEG: Post-Launch Evidence Generation

PMBCL: Primary Mediastinal Large B-cell Lymphoma

QALYs: Quality Adjusted Life Years

RCTs: Randomised Control Trials

RWD: Real World Data

RWE: Real-World Evidence

SBU: Swedish Agency for Health Technology Assessment and Assessment of Social Services

SL: List of Specialties

SMA: Spinal Muscular Atrophy

SMR: Service Médical Rendu (Medical Benefit)

TAV: Therapeutic Added Value

TGA: Therapeutic Goods Administration

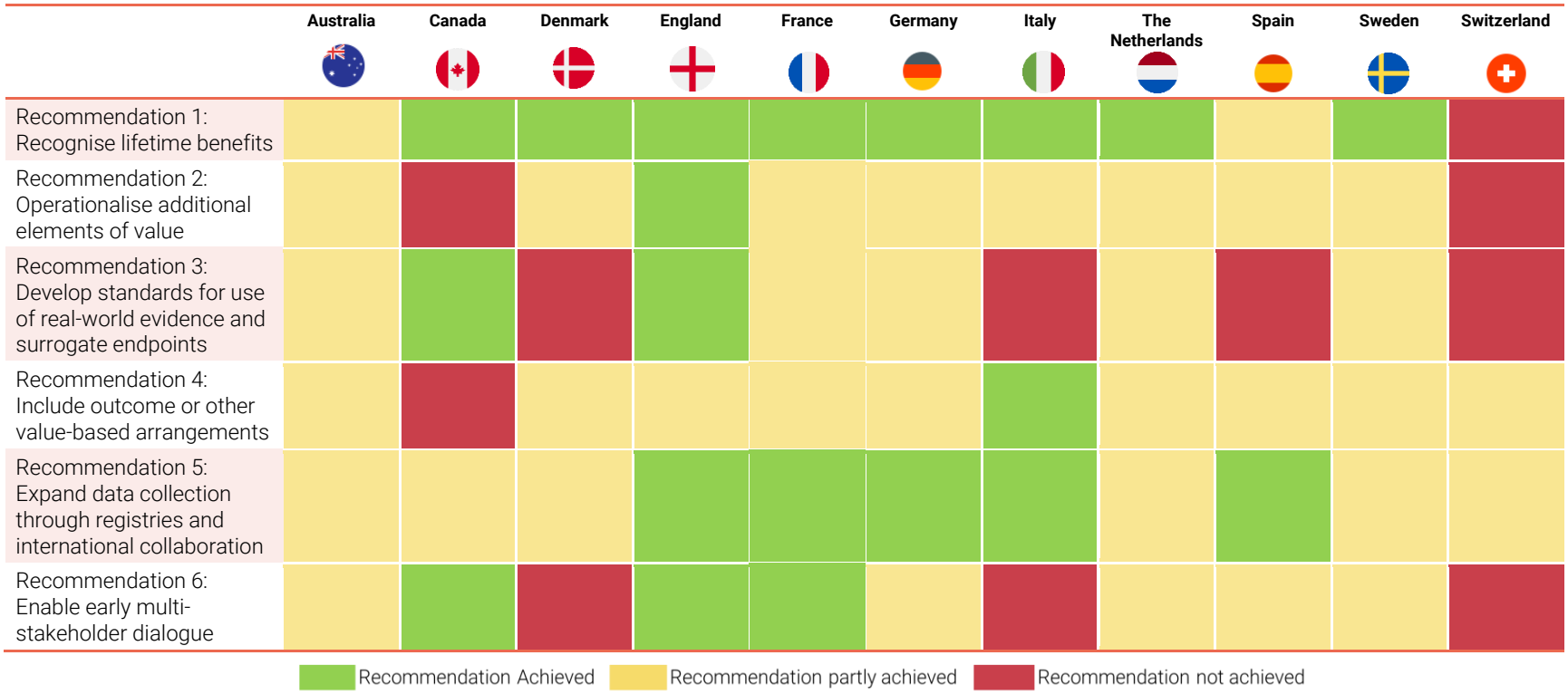
TLV: Tandvårds- och läkemedelsförmånsverket

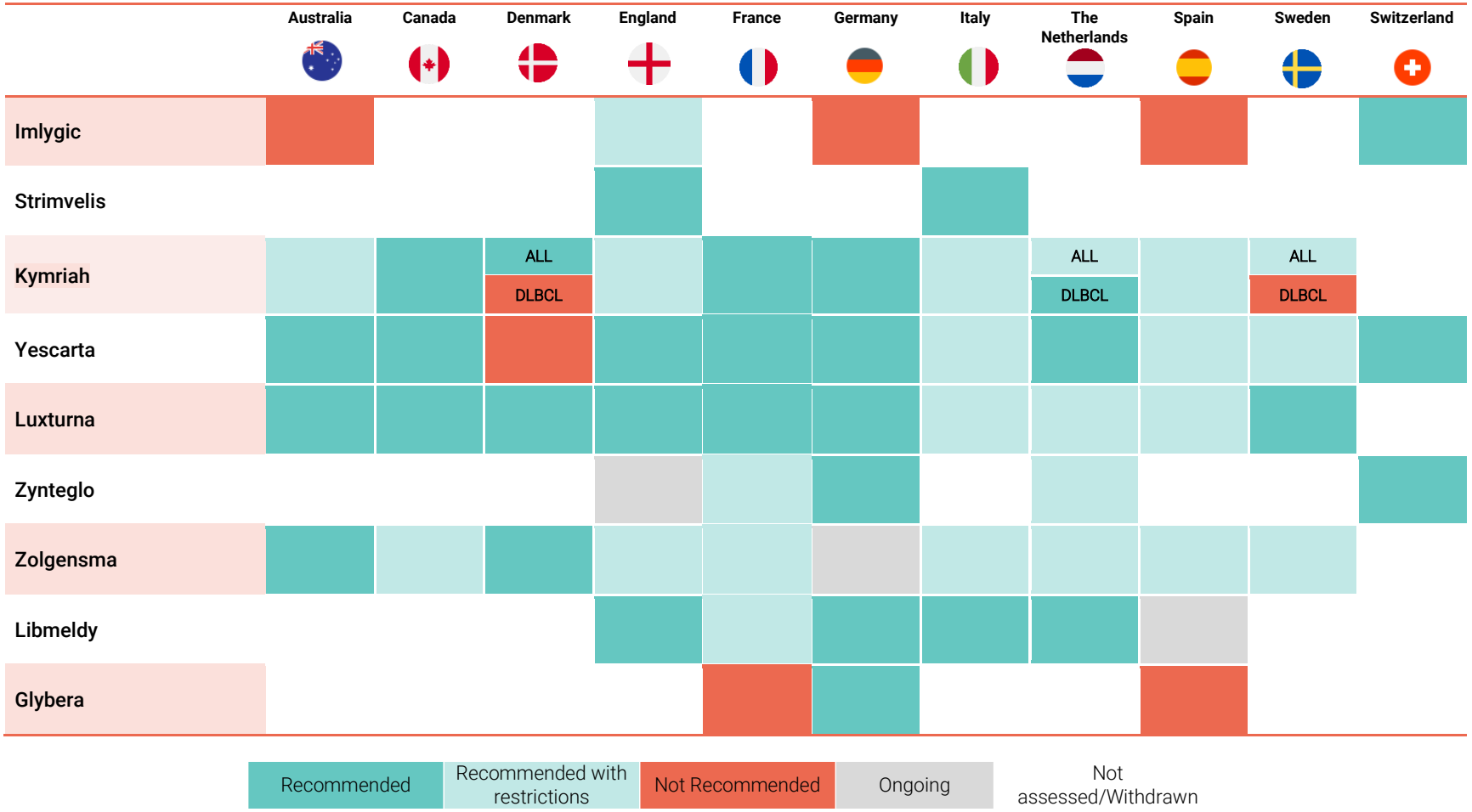
WTP: Willingness to Pay

ZIN: Zorginstituut Nederland

Executive Summary

In a previous report, 'Health Technology of Gene Therapies: Are Our Methods Fit for Purpose?' (Besley et al., 2022), we explored the challenges for health technology assessment (HTA) of gene therapies. Via evidence review, analysis, and discussions with experts, we arrived at six recommendations that specify the changes to HTA methodologies and evidence generation activities that should be prioritised to enable the full value of gene therapies to be captured in HTA. This report explores the extent to which these recommendations are being achieved in nine European countries plus Australia and Canada and identifies areas of best practice. The tables below provide a high-level overview of the level of achievement to date and HTA outcomes for a selection of gene therapies in each country.




Australia
Canada
Denmark
England
France
Germany
Italy
The Netherlands
Spain
Sweden
Switzerland
Imlygic
Strimvelis
Kymriah
ALL
DLBCL
ALL
DLBCL
ALL
DLBCL
Yescarta
Luxturna
Zynteglo
Zolgensma
Libmeldy
Glybera
Recommended
Recommended with restrictions
Not Recommended
Ongoing
Not assessed/Withdrawn

1. Background

Gene therapies have the potential to offer transformational benefits to patients, as well as further benefits for health systems and society. However, there are several challenges preventing timely patient access. The challenges of health technology assessment (HTA) of gene therapies alongside potential solutions are set out and discussed in a report commissioned by Pfizer (Besley et al., 2022), which can be found here. Based on a review of the literature, supplemented by the insights and discussions of an international panel of HTA and health economics experts, the authors arrive at six overarching recommendations (see Box 1). The recommendations highlight the changes to HTA methodologies as well as evidence generation activities that should be prioritised to enable the potential benefits of gene therapies to be realised.

As discussed by Besley et al. (2022), the first two recommendations address challenges in fully capturing the potential value of gene therapies as part of the HTA process. The final four recommendations aim to improve the quality and acceptability of the evidence generated and to provide methods for handling residual uncertainty. The recommendations are not specific to the HTA of gene therapies and should be consistently applied across HTA of other treatments. However, due to the combination of challenges presented by the HTA of gene therapies, if implemented, the recommendations are likely to have a larger impact on the assessment of gene therapies.

BOX 1: RECOMMENDATIONS FOR HTA OF GENE THERAPIES

RECOMMENDATIONS TO BETTER CAPTURE THE VALUE OF GENE THERAPIES:

1. Incorporate methods to recognise the potential lifetime benefits of gene therapies by including a lifetime perspective in modelling accompanied by sensitivity analysis including of the discount rate.
2. Operationalise additional elements of value as part of the decision-making process within HTA, on the basis of continued research.

RECOMMENDATIONS TO ADDRESS UNCERTAINTY IN OUTCOMES:

3. Develop transparent standards for the inclusion of real-world evidence (RWE) and surrogate endpoints in HTA.
4. Include outcomes-based arrangements or other value-based arrangements as part of or following HTA to mitigate uncertainty in long term outcomes whilst enabling patient access.
5. Expand data collection through registries and international collaboration.
6. Enable early multi-stakeholder dialogue, including patient representatives, to align on feasible and appropriate HTA evidence packages.

This document sets out to what extent the recommendations are being achieved in a selection of European countries, Australia and Canada. We also reviewed the HTA outcomes of key gene therapies that have been conducted in these countries to help with further understanding of the current state of play.

2. Methodology

2.1 HTA outcomes

The European Medicines Agency (EMA) defines gene therapies (or gene therapy medicinal products/GTMPs) as medicines which "contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases" (EMA, 2023). In our assessment of HTA outcomes, we assess technologies defined as gene therapies by the EMA. We assess the outcomes of the HTA of Glybera® (as the first gene therapy given marketing authorisation by the EMA, despite its subsequent withdrawal by the manufacturer because of high price and limitations in use (Pochopień et al., 2021)) and the gene therapies with an active EMA marketing authorisation in December 2021, namely Imlygic®, Strimvelis®, Kymriah®, Yescarta®, Luxturna®, Zynteglo® (subsequently withdrawn by the manufacturer), Zolgensma® and Libmeldy®.

To gather the HTA outcomes of the relevant gene therapies in each country, we first looked at the relevant country's HTA body (or other relevant government body/health system) website. In the absence of a publicly available outcome on the HTA body's website, we next looked to peer-reviewed publications. Where HTA documentations were not available in English, we used online translation services, and these outcomes were verified by Pfizer's local country affiliates.

Table 1 shows the various potential outcomes of HTA assessment used in this report.

TABLE 1: HTA OUTCOME DESCRIPTIONS

Outcome	Description
Recommended	Positive HTA recommendation or equivalent*
Recommended with restriction	Restricted HTA recommendation (typically recommended for a subpopulation compared to the marketing authorisation)
Not recommended	Negative HTA recommendation or equivalent**
Not assessed	No HTA conducted or equivalent
Ongoing	HTA appraisal ongoing at time of search
Withdrawn	Marketing authorisation withdrawn before HTA could be completed.

*In Germany, a conclusion of any level of added benefit. In Switzerland, inclusion on the List of Specialties.
**In Germany, a conclusion of no added benefit. In Switzerland, we are only able to determine if something is included on the List of Specialties or not. We are not able to determine whether a technology has been assessed and a decision made not to recommend for inclusion on the list.

2.2 Achievement of recommendations

To determine the progress of each country towards achieving each recommendation, we conducted targeted literature searches, including searches of grey literature and official HTA agency documentation. We also incorporated input from the experts that participated in the roundtable that informed our original report (Besley et al., 2022), as well as input from Pfizer's local country affiliates. This input enabled us to consider the extent that policies or guidelines were used in practice.

Table 2 shows the three levels used to assess whether the recommendations have been achieved. The choice of level for each country and recommendation is a necessary judgment made more difficult because of variable amounts of information available via a range of sources. In each case, the summary of details that underpin these judgements are provided in the corresponding country sections. We attempted to appraise differences between HTA guidance and the reality of HTA appraisals in practice where possible, but this is not likely to have been fully captured. Furthermore, the presence of confidential discounts to list price is likely to have a considerable impact on the outcomes of HTA in practice, which cannot be captured in our analysis.

TABLE 2: LEVELS OF RECOMMENDATION ACHIEVEMENT DESCRIPTION

Category	Description
Recommendation achieved	The recommendation has been considered, and relevant guidelines/agreements are routinely implemented. However, this does not preclude further improvements.
Recommendation partly achieved	Steps have been taken to begin implementing the recommendation or implementation has begun, but uptake could be improved considerably.
Recommendation not achieved	No steps have been taken to begin implementation of the recommendation.

2.3 Identifying areas of best practice

Using the assessment of progress towards achieving each recommendation in each country (section 2.2), we identified areas of strength across the full set of countries. These are highlighted as areas of best practice. Note that demonstrating best practice for a recommendation (or part of a recommendation) does not mean there is no further room for improvement.

The purpose of providing these examples is to demonstrate that progress against each of these recommendations is achievable and not to suggest that every country should follow the highlighted approach. Different approaches will suit different approaches to HTA, pricing and reimbursement processes and health financing models that vary significantly between countries.

3 Areas of Best Practice

In this chapter, we present the results of the best practice analysis. More information on each example can be found by following the link to the relevant country scorecard.

Recommendation 1: Recognise lifetime benefits

Recommendation achieved by: 

Achievement of this recommendation requires that i) the HTA body or equivalent recommends the use of a lifetime horizon for the models produced for an economic evaluation and ii) the HTA body or equivalent provides guidance on the use of discount rates, including some allowance for the incorporation of alternative discount rates for long-term benefits (for example by including an option for a lower discount rate in future years, beyond a given threshold, or via sensitivity analysis).

CADTH (Canada), DMC (Denmark), NICE (England), HAS (France), and AIFA (Italy) allow for the time horizon to be long enough to reflect all significant differences in costs and outcomes (CADTH, 2018; DMC, 2021c; NICE, 2022b; HAS, 2020a; AIFA, 2020a). ZIN (the Netherlands) mandates the use of a lifetime horizon (National Health Care Institute, 2016). Both approaches are considered sufficient to represent best practice.

Best practice on discount rates is modelled by HAS (France), which recommends the use of a 1.5% discount rate for costs and benefits after 30 years (HAS, 2020a), and by NICE (England), which recommend the use of a reduced discount rate of 1.5% for costs and benefits for technologies that meet specific criteria (including the criterion that the benefits must be sustained over a long period of time), (NICE, 2022b). Similarly, TLV (Sweden), AIFA (Italy), IQWiG (Germany) and CADTH (Canada) recommend the use of sensitivity analysis to explore the impact of the base case discount rate (TLV, 2003; AIFA, 2020a; IQWiG, 2022a; CADTH, 2022a). Guidance recommending the use of differential discounting is particularly advanced in the Netherlands (Versteegh, Knies and Brouwer, 2016).

Recommendation 2: Operationalise additional elements of value

Recommendation achieved by: 

This recommendation requires that the HTA body or equivalent explicitly recognises additional elements of value (e.g., severity, rarity, equity, unmet need, innovation).[1] Where included, additional value elements may be implemented in a variety of ways, e.g., via an increase to the cost-effectiveness threshold, adaptive pathways or deliberative processes, and this must be consistent across all technologies being evaluated.

Examples are provided by NICE (England), which considers severity via a severity modifier that provides an increased weighting of quality-adjusted life years (QALYs) for severe diseases (NICE, 2022b); G-BA (Germany), which assesses rare disease treatments via an orphan medicines pathway

[1] Note that the recommendation does not mandate that all potential value elements (e.g. those considered in the 'value flower' (Lakdawalla et al., 2018)) are included. This is because value judgments are subjective and context specific, thus not all potential elements of value will be relevant in every country.

that subjects treatment to more simplified evidentiary requirements (Nicod et al., 2020); and AIFA (Italy) which assesses and classifies technologies by level of innovation (AIFA, 2018, 2020b).

None of the countries studied consider all potentially relevant elements of value. Yet, England was judged as achieving this recommendation due to NICE's willingness to incorporate a number of additional elements of value and the methods put in place to ensure that many of these value elements are considered consistently across technologies.

Recommendation 3: Develop standards for inclusion of real-world evidence (RWE) and surrogate endpoints

Recommendation achieved by: 

This recommendation requires that the HTA body or equivalent provides detailed guidance on the suitability and use of surrogate endpoints and RWE, including details of the circumstances when the inclusion of these in HTA is deemed appropriate. For surrogate endpoints, the guidance should include information on acceptable validation techniques, and for RWE, it should include processes for transforming real-world data into RWE. Good examples are provided by CADTH (Canada), which provides detailed guidance on surrogate outcomes (CADTH, 2023), and NICE (England), which provides an RWE framework (NICE, 2022c).

Going forwards, with joint clinical assessments on the horizon, a shared commitment to recognising and validating surrogate endpoints and implementing RWE standards will be increasingly important. This should also include generating alignment across regulatory and HTA bodies.

Recommendation 4: Include outcome or other value-based arrangements

Recommendation achieved by: 

This recommendation requires that mechanisms for outcomes-based or value-based agreements to be negotiated are in place and routinely implemented. Examples of potential arrangements include performance or outcomes-based payments and coverage with evidence development.

Italy is judged as achieving this recommendation as many outcomes-based and economic risk-sharing agreements have been implemented, making use of their well-established registries. In addition, staged payments linked to individual patient outcomes are being used for two gene therapies. However, we recognise that recently there has been a decline in the use of outcome-based payments in Italy in favour of confidential price discounts (Cole, Neri and Cookson, 2021).

Recommendation 5: Expand data collection through registries and international collaboration

Recommendation achieved by: 

The existence of national registries demonstrates the presence of infrastructure for generating RWE. Such registries can provide initial evidence of clinical effectiveness and/or support post-approval

evidence generation to address uncertainties and/or provide data to support financial agreements as part of recommendation 4.[2]

Examples are provided by France, which has a national database for rare disease (BNDMR) (FIMATHO, 2022), and Denmark, which has a nationwide hospital registry (Danish National Patient Registry, DNPR) (Lynge, Sandegaard and Rebolj, 2011) and a registry for patients with rare and/or hereditary eye diseases that is being used for the outcomes-based agreement in place for Luxturna (Bartels et al., 2022). Italy has a number of AIFA monitoring registries where data on the use of products has been routinely collected (AIFA, 2022).

International collaboration can be achieved through engagement by any stakeholder in the development of international registries or by involvement of the HTA body (or equivalent) in national and international collaborations linked to the use of registry data.

Examples include engagement in EUnetHTA (European Network for Health Technology Assessment) post-launch evidence generation (PLEG) pilots, such as:

- the pilot on Left ventricular Assist Devices on patients with end-stage heart failure involving NICE (England), Avalia-t (Galician Agency for Health Knowledge Management, Spain) and Agenas (Italian National Agency for Regional Health Services, Italy).

- the assessment of the suitability of the European Cystic Fibrosis Society Patient Registry (ECFSPR) (involving HAS (France), and ZIN (the Netherlands)) and the European Society for Blood and Marrow Transplantation (EBMT) CAR-T products registry (involving AIFA (Italy), G-BA (Germany), HAS (France), NICE (England), and ZIN (the Netherlands)) across a number of indications.

Recommendation 6: Enable early multi-stakeholder dialogue

Elements of best practice demonstrated by: 

This recommendation requires that the HTA body or equivalent has mechanisms/pathways in place to facilitate early scientific dialogue, incorporating all relevant stakeholders, which includes patient representatives.

The availability of joint scientific advice, e.g., in partnership with regulators or another HTA body, is particularly advanced, such as the parallel advice offered by CADTH (Canada) and NICE (England) (CADTH, 2019c; NICE, 2022b) and the joint consultations available through the EUnetHTA that include HAS (France), IQWiG (Germany), G-BA (Germany), AIFA (Italy), AEMPS (Spain), TLV (Sweden) and ZIN (the Netherlands).

[2] *Note we do not assess the quality of any specific registry but highlight where registry data is being considered in relation to an initial HTA decision (or equivalent) or post-launch evidence generation.*

4 Country Scorecards

4.1 Australia

HTA Agency: **Pharmaceutical Benefits Advisory Committee (PBAC)/ Medical Services Advisory Committee (MSAC)**[3]

Main type of analysis: **Cost-effectiveness analysis**

TABLE 3: OUTCOMES OF HTA OF GENE THERAPIES - AUSTRALIA

GENE THERAPY (INTERNATIONAL NON-PROPRIETARY NAME/INN)	GENE THERAPY (BRAND NAME)	HTA RECOMMENDATION / REIMBURSEMENT DECISION	ADDITIONAL COMMENTS
Talimogene Laherparepvec	Imlygic®	Not recommended and not reimbursed - Appraised by PBAC (O'Sullivan, Philips and Rasko, 2022)	"Highly uncertain magnitude of clinical benefit, and thus highly uncertain cost-effectiveness" (PBAC, 2016b)
Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	Strimvelis®	Not assessed and not reimbursed	No listing on the Therapeutic Goods Administration (TGA - Australian regulatory agency) website (TGA, 2021)
Tisagenlecleucel	Kymriah®	Recommended with restrictions and Reimbursed - Appraised by MSAC	Publicly funded jointly by the Australian Government and states via NHRA (O'Sullivan, Philips and Rasko, 2022).
Axicabtagene ciloleucel	Yescarta®	Recommended and Reimbursed - Appraised by MSAC	Publicly funded via NHRA (O'Sullivan, Philips and Rasko, 2022)
Voretigene neparvovec	Luxturna®	Recommended and Reimbursed - Appraised by MSAC	Publicly funded via NHRA (O'Sullivan, Philips and Rasko, 2022)
Betibeglogene autotemcel	Zynteglo®	Not assessed and not reimbursed	No listing on the TGA website (TGA, 2021)
Onasemnogene abeparvovec	Zolgensma®	Recommended and Reimbursed Appraised by PBAC	Initial broad population refined based on regulatory label and then severity (using criteria established for comparator nusinersen). Listed on the PBS (Pharmaceutical Benefits Scheme, 2022).
Autologous CD34+ cells encoding ARSA gene	Libmeldy®	Not assessed and not reimbursed	No listing on the TGA website (TGA, 2021)
Alipogene tiparvovec	Glybera®	Not assessed and not reimbursed	No listing on the TGA website (TGA, 2021)

[3] The role of the Pharmaceutical Benefits Advisory Committee (PBAC) is to recommend medicines for listing on the Pharmaceutical Benefits Scheme (PBS), and vaccines for listing on the National Immunisation Program (NIP). The Medical Services Advisory Committee (MSAC) is responsible for evaluating medical services, technologies, and procedures. More recently, MSAC's responsibilities have expanded to include highly specialised therapies such as CAR-T, certain gene therapies and blood products.

TABLE 4: ACHIEVEMENT OF RECOMMENDATIONS TO DATE - AUSTRALIA

ACHIEVEMENT OF RECOMMENDATIONS TO DATE	JUSTIFICATION
Recommendation 1: Recognise lifetime benefits	- In May 2022, the Australian Government commissioned a report to evaluate the PBAC's current discount rate (5% for costs and benefits). The report found that there may be an argument for decreasing the discount rate (Medicines Australia, 2022b). - Medicines Australia (MA, local trade body) found that the PBAC's discount rate was the highest of the 40 countries reviewed (Medicines Australia, 2022b). - The matter was considered by the PBAC in July 2022, which recommended that the Government make a broader policy decision to change the standard base-case discount rate and that the discount rate be no lower than 3.5% per year (PBAC, 2022). A mandatory sensitivity analysis would still need to be conducted at 5% (PBAC, 2022). - In economic modelling, the PBAC guidelines allow a lifetime horizon to be utilised (PBAC, 2016a); however, in practice, there is a preference for the duration of available data to be used in base case analyses.
Recommendation 2: Operationalise additional elements of value	- In most circumstances, the PBAC only permits additional value elements to be incorporated as sensitivity analyses. The most common are adherence-improving factors, fear of contagion, equity, scientific spillovers and the impact on carers. - PBAC guidelines (PBAC, 2016a) state that "other less-quantifiable factors can also influence PBAC decision-making" including the severity of the medical condition treated. - In comparison, the Medical Services Advisory Committee (MSAC), which assesses medical technologies, allow the presentation of non-health benefits in the "Value of Knowing" section of their guidelines (MSAC, 2021). - Overall, additional value elements are considered implicitly by the PBAC, but they may need to consider incorporating these factors directly in order to ensure consistency and transparency in decision-making.
Recommendation 3: Develop standards for inclusion of RWE and surrogate endpoints	Surrogate Endpoints: - The PBAC have detailed guidelines for the use of surrogate outcomes (Grigore et al., 2020). Real-World Evidence: - The PBAC also allow for the inclusion of RWE but has a preference for randomised evidence (PBAC, 2016a). The PBAC guidelines include guidance on both methodological issues surrounding nonrandomised studies and sources of real-world data (RWD) for estimating utilisation (PBAC, 2016a). - They have previously approved medicines based on single-arm trials with external RWE comparator data (Medicines Australia, 2020). - However, there could still be considerable improvements in the collection and use of RWE in decision-making. This is supported by IQVIA research that found only 5% of PBAC submissions included RWE compared to 55% and 47% in UK and France, respectively (IQVIA and Medicines Australia, 2020).

Recommendation 4: Include outcome or other value-based arrangements	- PBAC guidelines for the implementation of outcome or value-based schemes are available (PBAC, 2016a). - Historically, outcome-based schemes in which the price or level of reimbursement is tied to achieving intermediate or final clinical endpoints have rarely been used in Australia (Lu et al., 2015). - However, such schemes are becoming more commonplace with the introduction of novel therapies; the two gene therapies reimbursed in Australia (Zolgensma® (PBAC, 2020), Luxturna® (MSAC, 2020)) were recommended with outcomes-based agreements.
Recommendation 5: Expand data collection through registries and international collaboration	- The Australian Bleeding Disorders Registry (ABDR) is used on a daily basis by clinicians in all Australian haemophilia treatment centres to assist in managing the treatment of people with bleeding disorders and to gain a better understanding of the incidence and prevalence of bleeding disorders, including the demand for, and to facilitate ordering of, clotting factor product. First developed in 1995, the ABDR is managed in collaboration with the Australian Haemophilia Centre Directors' Organisation (AHCDO), Haemophilia Foundation Australia and all Australian governments and is overseen by a Steering Committee (National Blood Authority, 2023). - The Australian Neuromuscular Disease Registry (ANMDR) is run through the Murdoch Children's Research Institute (MCRI) in Melbourne. In 2021, 448 Australians with neuromuscular disease were registered, with support provided by neuromuscular clinicians. The ANMDR has partnered with Muscular Dystrophy NSW (MDNSW), in addition to affiliations with the international organisation TREAT-NMD, the Australasian Neuromuscular Network (ANN), and the Save Our Sons (SOS) Duchenne Foundation. - Where evidence is uncertain but the technology itself is promising, funders may recommend funding on an interim basis. Scott (2017) found that MSAC used an interim funding mechanism for only 17 out of all 173 assessments between 1998 and 2015. Furthermore, 11 of the 17 interim funding decisions were subsequently reassessed. Two of these relied on registry evidence to provide Australian-specific data for addressing uncertainties around long-term safety, effectiveness and cost-effectiveness. This suggests that data from registries are often not included in HTA.
Recommendation 6: Enable early multi-stakeholder dialogue	- Alliance groups have been established to provide a coordinated voice on key issues related to genomics and gene therapy readiness in Australia and to help coordinate discussions with key stakeholders. - As part of the Strategic Agreement between MA and the Commonwealth, there is a commitment to establish an annual Horizon Scanning Forum and a Horizon Scanning Process to allow sufficient time to prepare for reimbursement of high-cost, highly specialised therapies. The inaugural MA Horizon Scanning Forum was held in December 2022 (Medicines Australia, 2022a). - The PBAC, MSAC and National Blood Authority (NBA) allow manufacturers to utilise pre-submission meetings to discuss upcoming products and gain early, non-binding advice with respect to reimbursement (PBS, 2022).

4.2 Canada

HTA Agency: **Canada's Drug and Health Technology Agency (CADTH)**[4]

Main type of analysis: **Cost-effectiveness analysis**

TABLE 5: OUTCOMES OF HTA OF GENE THERAPIES - CANADA

GENE THERAPY (INTERNATIONAL NON-PROPRIETARY NAME/INN)	GENE THERAPY (BRAND NAME)	HTA DECISION	ADDITIONAL COMMENTS
Talimogene Laherparepvec	Imlygic®	Not assessed	
Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	Strimvelis®	Not assessed	
Tisagenlecleucel	Kymriah®	Recommended (with price reduction)	The evaluation documents stated that for adults with DLBCL (Diffuse large B-cell lymphoma) a price reduction of at least 45% would be required to achieve an ICER (Incremental Cost-Effectiveness Ratio) $50,000 per QALY gained (CADTH, 2019d). For children and young adults with ALL (B-cell acute lymphoblastic leukaemia), the evaluation documents stated that a price reduction of at least 10% would be required to ensure the ICER is below $50,000 per QALY (CADTH, 2019d).
Axicabtagene ciloleucel	Yescarta®	Recommended (with price reduction)	The evaluation documents stated that estimated ICER was $226k when compared to best supportive care (CADTH, 2019a), and therefore, a price reduction was required.
Voretigene neparvovec	Luxturna®	Recommended (with price reduction)	The evaluation documents stated that a price reduction of more than 74% would be required to achieve ICERs below $50,000 per QALY (CADTH, 2020a).
Betibeglogene autotemcel	Zynteglo®	Not assessed	

[4] CADTH is the HTA agency for all provinces apart from Quebec. The HTA Agency for Quebec is Institut national d'excellence en santé et en services sociaux (INESSS). The information provided in this document relates to HTA by CADTH.

GENE THERAPY (INTERNATIONAL NON-PROPRIETARY NAME/INN)	GENE THERAPY (BRAND NAME)	HTA DECISION	ADDITIONAL COMMENTS
Onasemnogene abeparvovec	Zolgensma®	Recommended (with restriction and price reduction)	Initiation criteria and prescribing criteria related to the restriction can be found in the evaluation documents (CADTH, 2021). These evaluation documents stated that a price reduction of at least 90% was required for onasemnogene abeparvovec to achieve an ICER below $50,000 per QALY gained (CADTH, 2021).
Autologous CD34+ cells encoding ARSA gene	Libmeldy®	Not assessed	
Alipogene tiparvovec	Glybera®	Not assessed	

TABLE 6: ACHIEVEMENT OF RECOMMENDATIONS TO DATE - CANADA

ACHIEVEMENT OF RECOMMENDATIONS TO DATE	JUSTIFICATION
Recommendation 1: Recognise lifetime benefits	In economic evaluations: - For costs and benefits occurring beyond one year, the base case must use a discount rate of 1.5% for both costs and QALYs. The impact of uncertainty in the discount rate should be assessed through comparisons with non-reference case analyses using discount rates of 0% and 3% per year (CADTH, 2022a). - In the reference case, the time horizon should be long enough to capture all relevant differences in the future costs and outcomes associated with the interventions being compared (CADTH, 2018). Therefore, this does not rule out the use of a lifetime time horizon.
Recommendation 2: Operationalise additional elements of value	- All potential elements of value could be considered as part of the deliberative decision-making process. There is no formal mechanism for the inclusion of additional elements of value. - The deliberative nature of the process for potentially including additional elements of value means it can be unclear which value elements have been considered and whether they are considered consistently. - Attempts have been made to do multi-criteria decision analysis (MCDA) to determine key factors that should be considered in a reimbursement decision for rare diseases, with the corresponding weights. These trials have not been integrated into practice. - Research has been conducted exploring what Canadians value, with severity being an additional element of value that is highly valued by the Canadian public (Rizzardo et al., 2019). This demonstrates that Canadians do have preferences regarding additional value elements which could be operationalised within economic evaluations.

Recommendation 3: Develop standards for inclusion of RWE and surrogate endpoints	Surrogate endpoints: - CADTH has guidelines on the use of surrogate outcomes (Grigore et al., 2020). - CADTH has provided a discussion of the acceptability of surrogate outcomes according to their correlation with patient outcomes and the treatment intent (curative, adjuvant or palliative) in oncology (Grigore et al., 2020). - The use of surrogate endpoints is an example of a factor that is considered to lead to significant uncertainty. In the presence of unmet need, CADTH may provide a recommendation with restrictions despite this uncertainty (CADTH, 2022a) Real-World Evidence: - CADTH has published guidance for reporting real-world evidence (CADTH, 2023). - CADTH has also expanded their scientific advice program to include applications for advice on RWE generation plans after protocols for pivotal trials have been finalised. Rare diseases will be prioritised for this advice (CADTH, 2022b).
Recommendation 4: Enable outcome or other value-based arrangements	- Single list prices are regulated at the federal level, but negotiation of net prices, including any outcome-based contracts, operate at the regional level and are confidential (Paris and Belloni, 2014; Facey et al., 2021). There is no evidence of the use of these agreements.
Recommendation 5: Expand data collection through registries and international collaboration	- Patient registries exist for many disease areas, including lymphadema, neuromuscular disease and cystic fibrosis. - Although not specific to gene therapies, the Fabry's disease registry has been highlighted for its ability to allow for the ongoing development of robust data on natural history, treatment response, and it's potential for post-therapy evaluation of both effectiveness and adverse events. - There is a national cancer registry (the Canadian Cancer Registry; CCR) that primarily collects cancer incidence data. - Obtaining data can be difficult due to the regional fragmentation of electronic medical records (Cole, Neri and Cookson, 2021).
Recommendation 6: Enable early multi-stakeholder dialogue	CADTH offers three routes for early multi-stakeholder dialogue (CADTH, 2020b) : - CADTH only advice - Parallel advice with Health Canada and the Institut national d'excellence en santé et en services sociaux (INESSS) (currently in an observatory role) (CADTH, 2019b). - Parallel advice with the National Institute for Health and Care Excellence (NICE) in the UK (NICE, 2022a; CADTH, 2019c). Patients are engaged in early scientific advice by CADTH in two phases (CADTH, 2015): - Information submitted by the applicant in the briefing book: Applicants detail the patient or patient group engagement undertaken. - Patient interview: CADTH interviews a patient representative to capture information on current therapies and needs unmet by current therapies.

4.3 Denmark

HTA Agency: **Danish Medicines Council (DMC)** - Medicinrådet[5]

Main type of analysis: **Cost Effectiveness Analysis**

TABLE 7: OUTCOMES OF HTA OF GENE THERAPIES - DENMARK

GENE THERAPY (INTERNATIONAL NON-PROPRIETARY NAME OR INN)	GENE THERAPY (BRAND NAME)	HTA DECISION	ADDITIONAL COMMENTS
Talimogene Laherparepvec	Imlygic®	Not assessed	
Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	Strimvelis®	Not assessed	
Tisagenlecleucel	Kymriah®	ALL – Positive recommendation (DMC, 2019c) DLBCL – Negative recommendation (DMC, 2019d)	
Axicabtagene ciloleucel	Yescarta®	Negative recommendation (DMC, 2019a).	
Voretigene neparvovec	Luxturna®	Positive recommendation	Luxturna was originally not recommended due to high costs, uncertainty regarding the long-term effect and possible side effects. The positive recommendation was given after the inclusion of an outcomes-based payment agreement (DMC, 2020).
Betibeglogene autotemcel	Zynteglo®	Application withdrawn by manufacturer.	Bluebird bio was invited to enter joint negotiations with Nordic (Denmark, Finland, Iceland, Norway and Sweden) collaboration (EVERSANA, 2020A).
Onasemnogene abeparvovec	Zolgensma®	Positive recommendation (DMC, 2021a)	
Autologous CD34+ cells encoding ARSA gene	Libmeldy®	Not assessed	
Alipogene tiparvovec	Glybera®	Not assessed	

[5] *The DMC conducts HTA of medicines. In 2021 the Danish Health Technology Council conducts HTA of MedTech. As the aim of this report is to consider HTA of gene therapies, we will consider our recommendations looking at decisions and methods of the DMC only.*

TABLE 8: ACHIEVEMENT OF RECOMMENDATIONS TO DATE - DENMARK[6]

ACHIEVEMENT OF RECOMMENDATIONS TO DATE	JUSTIFICATION
Recommendation 1: Recognise lifetime benefits	In Economic Evaluations (DMC, 2021b): - The DMC recommends the use of the socio-economic discount rate from the Danish Ministry of Finance. - The discount rates were updated in 2021 so that QALYs and costs occurring in the first 35 years should be discounted at 3.5%. Costs & QALYs realised between years 36 and 70 should be discounted at 2.5%, and costs and QALYs occurring beyond 70 years should be discounted at 1.5% (Danish Ministry of Finance, 2021). - The DMC guidelines state that 'The time horizon for the analysis should be long enough to catch all significant differences in effects and costs between the alternatives. This means that an extension of the time horizon would not affect the results to a significant degree.' Therefore, this does not rule out the use of a lifetime time horizon. - The DMC also advocate for deterministic sensitivity analysis of the time horizon.
Recommendation 2: Operationalise additional elements of value	Severity (DMC, 2019b) - There are special cases where the DMC can choose to include seriousness in its decision-making basis. This could be in situations where the new medicine: ▪ is aimed at children and young people (0-25 years) ▪ relates to illness with unusually early death ▪ cures, prevents or modifies chronic disability or other symptoms that are fundamentally life-limiting ▪ is aimed at serious and particularly infectious diseases ▪ is the only real disease-modifying or curative treatment. - The Council may also include seriousness in cases other than those mentioned above if it considers that other special issues apply to the disease, the patient group, society, the medicinal product or others. - Assessment as to whether severity should be considered in the evaluation is made via the council's deliberative process, where stakeholders are given the opportunity to participate and seek to reach a consensus (Wadmann and Højgaard, 2021). - Severity is included in the analysis qualitatively, and the DMC guidelines make no other references to additional elements of value.
Recommendation 3: Develop standards for inclusion of RWE and surrogate endpoints	Surrogate endpoints: - There are no guidelines for the use of surrogate outcomes (Grigore et al., 2020). Real-World Evidence: - The DMC's guidelines (DMC, 2021c) state that data from randomized controlled trials (RCTs) are preferred to RWE but include details of the information needed to support RWE if required. - Standards for surrogate endpoints and RWE should be significantly improved.

[6] *Our assessment of Denmark's achievements has heavily relied on the information published by the Danish Medicines Council (DMC) including in their guidelines* (DMC, 2021b). *However, it is worth noting that local experience suggests that the DMC has displayed willingness to be flexible on many aspects of the HTA process.*

Recommendation 4: Include outcome or other value-based arrangements	- The payment by results agreement for Luxturna® was the first outcomes-based payment model in Denmark (DMC, 2020). - According to comments made by Amgros (manages procurement for Danish public hospitals) and Novartis (manufacturer) at an ISPOR (The Professional Society for Health Economics and Outcomes Research) advanced therapy medicine product (ATMP) spotlight webinar the agreement has been a success so far (Bartels et al., 2022): ▪ AMGROS noted that despite a contract that is considerably larger than other pricing they have in place, the contract did not cover all scenarios, and they still have a lot to learn for the development of future agreements. ▪ AMGROS are developing new standard contracts for ATMPs which were due to be ready by the end of 2022, to work towards country-specific agreements which can form the basis of their discussions and negotiations with manufacturers. ▪ AMGROS also noted that there is some scepticism from the Danish Medicines Agency (DMA) on the use of outcomes-based agreements. ▪ This agreement is a start towards enabling payers to manage the risk of uncertainty in long-term outcomes. However, as noted, there is still progress that needs to be made towards developing and implementing these agreements.
Recommendation 5: Expand data collection through registries and international collaboration	- The DNPR is one of the world's oldest nationwide hospital registries and is used extensively for research (Lynge, Sandegaard and Rebolj, 2011). - Registry for patients with rare and/or hereditary eye diseases was in place before the recommendation of Luxturna, enabling better data collection for the outcomes-based payment agreement (Bartels et al., 2022). - However, when considered alongside the RWE guidelines, registry data is likely to be underutilised during HTA appraisals.
Recommendation 6: Enable early multi-stakeholder dialogue	- DMA have a National Scientific Advice service (DMA, 2018). - However, the service can only provide advice on clinical trials and regulatory issues and explicitly excludes issues related to Health Technology Assessment. - Furthermore, neither DMC nor DMA are part of EUnetHTA.

4.4 England

HTA Agency: National Institute for Health and Care Excellence (NICE)

Main type of analysis: Cost Effectiveness Analysis

TABLE 9: OUTCOMES OF HTA OF GENE THERAPIES - ENGLAND

GENE THERAPY (INTERNATIONAL NON-PROPRIETARY NAME OR INN)	GENE THERAPY (BRAND NAME)	HTA DECISION	ADDITIONAL COMMENTS
Talimogene Laherparepvec	Imlygic®	Recommended with restriction	Recommended only if: treatment with systemically administered immunotherapies is not considered the best option by a multidisciplinary team and the company provides the discount agreed in the patient access scheme (NICE, 2016).
Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	Strimvelis®	Recommended (Highly Specialised Technologies - HST)	Recommended through HST pathway (NICE, 2018b).
Tisagenlecleucel	Kymriah®	Funded via CDF (Cancer Drugs Fund) with CED (Coverage with Evidence Generation) scheme (for both indications*)	Access is provided whilst additional data is collected. Reassessment will take place after the evidence collection period (NICE, 2019a, 2018a).
Axicabtagene ciloleucel	Yescarta®	Recommended	Recommended based on additional data collected as part of the Cancer Drugs Fund (NICE, 2023)
Voretigene neparvovec	Luxturna®	Recommended (HST)	Recommended through HST pathway (NICE, 2019b)
Betibeglogene autotemcel	Zynteglo®	Suspended	HTA assessment suspended due to withdrawal of EMA marketing authorisation.
Onasemnogene abeparvovec	Zolgensma®	Recommended with restriction (HST)	Recommended for presymptomatic 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene in babies. Provided under a managed access agreement. Recommended with restriction for 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of type 1 SMA in babies, only if they are 6 months or younger, or they are aged 7 to 12 months, and their treatment is agreed by the

GENE THERAPY (INTERNATIONAL NON-PROPRIETARY NAME OR INN)	GENE THERAPY (BRAND NAME)	HTA DECISION	ADDITIONAL COMMENTS
			national multidisciplinary team. Provided under a simple price discount access scheme. No recommendation could be made for type 2 or 3 SMA with up to 3 copies of the SMN2 gene based on lack of evidence. (NICE, 2021).
Autologous CD34+ cells encoding ARSA gene	Libmeldy®	Recommended (HST)	Recommended through the HST pathway (NICE, 2022a).
Alipogene tiparvovec	Glybera®	Not assessed	

*ALL: B-cell acute lymphoblastic leukaemia. DLBCL: Diffuse large B-cell lymphoma

TABLE 10: ACHIEVEMENT OF RECOMMENDATIONS TO DATE - ENGLAND

ACHIEVEMENT OF RECOMMENDATIONS TO DATE	JUSTIFICATION
Recommendation 1: Recognise lifetime benefits	In economic evaluations: - NICE guidance requests a reference case discount rate for costs and benefits of 3.5% per year (NICE, 2022b). - NICE recommends a reduced discount rate (non-reference case discount rate) of 1.5% for both costs and benefits of treatments that are potentially curative (Coyle et al., 2020; Hettle et al., 2017). The criteria that must all be met for the use of non-reference-case discount rates are (NICE, 2022b): 1. The technology is for people who would otherwise die or have a very severely impaired life. 2. It is likely to restore them to full or near-full health. 3. The benefits are likely to be sustained over a very long period. - Costs and benefits should be estimated for long enough to reflect all important differences in costs or outcomes between the technologies being compared. Therefore, when the technology has an effect on costs and outcomes over a patient's lifetime, a lifetime horizon is likely to be most appropriate (NICE, 2022b).
Recommendation 2: Operationalise additional elements of value	In general (NICE, 2022b): – Health outcomes of carers can be included if relevant. – Severity is considered through a QALY weighting of up to 1.7 for severe diseases, replacing the previous increased threshold of £50,000 for drugs that met the end-of-life criteria. – Unmet need is reflected in the definition of severity (proportional/absolute shortfall calculated with reference to current treatment). – Equity may be considered qualitatively. – NICE's HST programme is an example of extra value (beyond the QALYs gained) being recognised for very rare technologies. The HST pathway offers a more pragmatic approach to dealing with uncertainty, as well as QALY weighting in circumstances when the

	health gains are substantial (greater than 10 QALYs expected be gained over a patient's lifetime, increasing the threshold to a maximum of £300,000). Specific to the assessment of gene therapies: – The Innovative Medicines Fund (IMF) was introduced as a key part of the health systems' readiness for the continued adoption of advanced therapy medicinal products. – Several gene therapies have been assessed using NICE's HST pathway. However, it is worth noting that HST's requirement for a small patient population may mean that gene therapies that target more common diseases will not benefit.
Recommendation 3: Develop standards for inclusion of RWE and surrogate endpoints	Surrogate Endpoints: - NICE guidelines on the use of surrogate outcomes focus on the "decision uncertainty associated with evidence, and this reflected in the economic modelling of a technology" and recommend that "in all cases, the uncertainty associated with the relationship between the end point and health-related quality of life or survival should be explored and quantified" (Grigore et al., 2020) - NICE has analysed the suitability of particular surrogate outcomes for oncology (Grigore et al., 2020) Real-World Evidence: - NICE's recently published real-world evidence framework (NICE, 2022c) is arguably the most comprehensive guideline for the inclusion of RWE in HTA.
Recommendation 4: Include outcome or other value-based arrangements	- While financial- and outcome-based arrangements are theoretically possible through patient access schemes and managed access arrangements, in practice, these are rarely implemented outside the context of the CDF, and HST (Marsh, 2018), and negotiations tend to fall back on simple price discounts. - Data tracking through the CDF, which enables value-based arrangements, demonstrates that it is possible, but national data collection outside of cancer is more limited, making such arrangements more difficult to implement. This may change following the introduction of the IMF, which applies more broadly than cancer (NHS England, 2021).
Recommendation 5: Expand data collection through registries and international collaboration	- NHS (National Health Service) England conducts clinical audits (providing snapshots of clinical care) and has registries in a limited number of disease areas and conditions (NHS Digital, 2022). - The National Cancer Registration and Analysis Service (NCRAS) is responsible for cancer registration in England (NHS Digital, 2022a). - The National Congenital Anomaly and Rare Diseases Registration Services (NCARDRS) records people with congenital abnormalities and rare diseases across England (NHS Digital, 2022b). - Through EUnetHTA, NICE is part of a PLEG pilot to address remaining uncertainties and gather additional data on the use of Left ventricular Assist Devices on patients with end-stage heart failure. The pilot is being undertaken in collaboration with Avalia-t, Agenas, and KCE (Belgian Health Care Knowledge Centre). - NICE is involved in a pilot (EUnetHTA, 2020a) to assess the suitability of the EBMT CAR-T products registry for ALL, DLBCL, primary mediastinal large B-cell lymphoma (PMBCL) for PLEG purposes in collaboration with a number of other agencies.
Recommendation 6: Enable early multi-stakeholder dialogue	NICE offers four routes for their scientific advice for pharmaceutical products (NICE, 2022b): 1. NICE only

	2. Parallel advice with CADTH (NICE, 2022a; CADTH, 2019c). 3. Parallel advice with the Medicines and Healthcare Products Regulatory Agency (MHRA). 4. Concurrent advice with the EMA regulatory process. As part of their scientific advice service, NICE will engage patient experts. (NICE, 2022c) Evidence suggests that the scientific advice given is either insufficient or in conflict with independent scientific advice manufacturers receive (Coyle et al., 2020). Therefore, despite this recommendation being achieved through providing opportunities for early-multi stakeholder dialogue that will include patient representatives, there are still improvements that need to be made to these services to ensure they provide sufficient meaningful advice to manufacturers.

4.5 France

HTA Agency: **Haute Autorité de Santé (HAS)**

Main type of analysis: **Medical benefit (SMR) and medical added benefit (ASMR)**

TABLE 11: OUTCOMES OF HTA OF GENE THERAPIES - FRANCE

GENE THERAPY (INTERNATIONAL NON-PROPRIETARY NAME OR INN)	GENE THERAPY (BRAND NAME)	HTA DECISION	ADDITIONAL COMMENTS
Talimogene Laherparepvec	Imlygic®	Not assessed	
Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	Strimvelis®	Not assessed	
Tisagenlecleucel	Kymriah®	Recommended (for both indications*) (HAS, 2021a; b)	
Axicabtagene ciloleucel	Yescarta®	Recommended (HAS, 2021d)	
Voretigene neparvovec	Luxturna®	Recommended (Gozzo et al., 2021)	
Betibeglogene autotemcel	Zynteglo®	Recommended with restriction	Favourable opinion for patients aged over 12 to under 35. Unfavourable for patients over 35 (Haute Autorité de Santé, 2020).
Onasemnogene abeparvovec	Zolgensma®	Recommended with restriction	Favourable opinion for SMA Type 1,2, and pre-symptomatic (reassessment after one year). Unfavourable opinion for SMA type 3. (Haute Autorité de Santé, 2020)
Autologous CD34+ cells encoding ARSA gene	Libmeldy®	Recommended with restriction	Reimbursed via early access authorisation only for asymptomatic children without clinical manifestation of metachromatic leukodystrophy (ASMR III). (Haute Autorité de Santé, 2022).
Alipogene tiparvovec	Glybera®	Not recommended	Conclusion that there was insufficient clinical benefit (Haute Autorité de Santé, 2016).

*ALL: B-cell acute lymphoblastic leukaemia, DLBCL: Diffuse large B-cell lymphoma

TABLE 12: ACHIEVEMENT OF RECOMMENDATIONS TO DATE - FRANCE

ACHIEVEMENT OF RECOMMENDATIONS TO DATE	JUSTIFICATION
Recommendation 1: Recognise lifetime benefits	In economic evaluations: - Costs and benefits should be discounted whenever the time horizon exceeds 12 months (HAS, 2020a). - Reference case analysis should use the public discount rate, determined by a group of experts, that is applied to all public investment decisions, for time horizons of less than 30 years (set at 2.5% since 2013). For time horizons beyond 30 years, the discount rate gradually decreases to a floor of 1.5% for both costs and benefits (HAS, 2020a). - Guidance recommends sensitivity analysis of the time horizon and discount rate (HAS, 2020a). - Time horizon may span an entire lifetime or a specified period, making a trade-off between ensuring information produced over the time horizon is sufficient for reflecting all differences in costs and health effects and uncertainty resulting from extrapolation of data over-time (HAS, 2020a).
Recommendation 2: Operationalise additional elements of value	In general (HAS, 2020a; b): - 'Seriousness of the disease' is considered in assessment of SMR and ASMR. - For SMR, other therapies available and 'public health benefit' in terms of unmet need are considered. For ASMR, Level of 'medical need' is considered. - Level of innovation is considered to be a determiner of ASMR, estimated through size of effect on health outcomes, severity and unmet need. - Local experience suggests caregiver burden has been incorporated in sensitivity analysis of economic models, but it is not systematically included.
Recommendation 3: Develop standards for inclusion of RWE and surrogate endpoints	Surrogate Outcomes: - HAS has guidance on the use of surrogate outcomes (Grigore et al., 2020). - Survival prediction criterion may be used in lieu of data to measure life-years if there is strong, established evidence of the predictiveness of this surrogate endpoint (HAS, 2020a). Real-World Evidence: - Traditionally HAS has considered randomised controlled trials (RCTs) as the gold standard and generally placed little weight on the inclusion of RWE for reimbursement decisions (HAS, 2020a). - For rare diseases, there is a process that allows for more leniency around the quality of evidence (Nicod et al., 2020). - In 2021, HAS provided methodological guidance for generating real-world evidence (HAS, 2021c). - Although HAS has published methodological recommendations for generating RWE (HAS, 2021c), expert observations suggest that RWE is still not widely accepted in submissions.

Recommendation 4: Include outcome or other value-based arrangements	- Population-based agreements (coverage with evidence development) have been used in France, for example, for Kymriah® (CAR-T cell) (Facey et al., 2021).
	- There is likely to be progress made towards achieving this recommendation over the coming years:
	  o A recent framework includes details on possible methodologies for contracting for ATMPs, including outcomes-based and spread payment models.
	  o The French Government's Social Security Finance Bill (PLFSS) 2023 [passed December 2022 (Alcimed, 2023)] proposes an innovative pricing model to alleviate the burden associated with the cost of innovative therapies at the hospital/health system level (Morris, 2022).

Recommendation 5: Expand data collection through registries and international collaboration	- France has a national database of rare diseases (BNDMR) which they aim to link with the claims database (FIMATHO, 2022). - The aim of the French Health Data Hub is to make it easier to share health data securely to support research and innovation and, therefore, improve the quality of care and patient support. - HAS is involved in a pilot (EUnetHTA, 2020b) to assess the suitability of the ECFSPR and the EBMT CAR-T products registry for ALL, DLBCL and PMBCL for post-launch evidence generation purposes in collaboration with a number of other agencies. - France and Finland are engaging in a 2-year collaboration (Findata, 2021) to share best practices and identify challenges along with solutions surrounding the running of national health data platforms and facilitate the use of secondary data. - For all the gene therapies assessed by HAS, HAS asked for data to be collected post-launch through registries.
Recommendation 6: Enable early multi-stakeholder dialogue	- HAS offers early dialogue (before the start of pivotal clinical trials) for innovative medical products or other technologies that have a new mechanism of action in areas of unmet need (HAS, 2016b). - One or more patients may be consulted by HAS as part of the early dialogue process (HAS, 2016b). - HAS is a part of EUnetHTA and engages with the Parallel EMA/EUnetHTA Joint Scientific Consultations (JSC) (EUnetHTA, 2021b), which provides a single gateway for manufacturers to discuss their evidence generation plans with multiple European HTA agencies and the EMA (HAS, 2016b). Patients/patient representatives are also invited to participate in this process on a routine basis (EUnetHTA, 2021b). However, only a limited number of JSCs are offered (EUnetHTA, 2021a). - Evidence suggests that the scientific advice given is either insufficient or in conflict with independent scientific advice manufacturers receive (Coyle et al., 2020). Therefore, despite this recommendation being achieved through providing opportunities for early-multi stakeholder dialogue that will include patient representatives, there are still improvements that need to be made to these services to ensure they provide sufficient meaningful advice to manufacturers.

4.6 Germany

HTA Agency: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) / Gemainsamer Bundesausschuss (G-BA)

Main type of analysis: Therapeutic Added Value (TAV)

TABLE 13: OUTCOMES OF HTA OF GENE THERAPIES- GERMANY

GENE THERAPY (INTERNATIONAL NON-PROPRIETARY NAME OR INN)	GENE THERAPY (BRAND NAME)	HTA DECISION	ADDITIONAL COMMENTS
Talimogene Laherparepvec	Imlygic®	Not proven (IQWiG, 2016)	
Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	Strimvelis®	Not assessed	
Tisagenlecleucel	Kymriah®	Non-quantifiable added benefit (for both indications*) (Gozzo et al., 2021)	
Axicabtagene ciloleucel	Yescarta®	Non-quantifiable added benefit (Gozzo et al., 2021)	
Voretigene neparvovec	Luxturna®	Considerable added benefit (Gozzo et al., 2021)	RCT evidence was available for this therapy, as such benefit was quantifiable (G-BA, 2022b)
Betibeglogene autotemcel	Zynteglo®	Non-quantifiable added benefit (Gozzo et al., 2021)	Assessed using the simplified benefit process for orphan drugs** (G-BA, 2020)
Onasemnogene abeparvovec	Zolgensma®	Ongoing	Mandated collection of RWE due to limited clinical data. Referred to Anwendungsbegleitende Datenerhebung (AbD) which mandates high evidence standards of data collection, e.g., good quality registry (G-BA, 2021c). Added benefit not proven based on current evidence and given that €50m sales is expected to be exceeded it does not meet the criteria for the simplified benefit process for orphan products** (G-BA, 2021a)

Gene Therapy (International nON-PROPRIETARY NAME or INN)	**GENE THERAPY (BRAND NAME)**	**HTA DECISION**	**ADDITIONAL COMMENTS**
Autologous CD34+ cells encoding ARSA gene	Libmeldy®	Major additional benefit (Children with late infantile (LI) or early juvenile (EJ) forms of metachromatic leukodystrophy (MLD) without clinical manifestations of the disease) & Non-quantifiable added benefit (Children with the EJ form of metachromatic leukodystrophy with early clinical manifestations of the disease who still have the ability to walk independently, before the onset of cognitive decline)	Assessed using the simplified benefit process for orphan drugs** (G-BA, 2021b)
Alipogene tiparvovec	Glybera®	Non-quantifiable added benefit (G-BA, 2023)	Subsequently withdrawn by the manufacturer

*ALL: B-cell acute lymphoblastic leukaemia. DLBCL: Diffuse large B-cell lymphoma
**All orphan products under €50m annual sales were automatically granted at least "non-quantifiable benefit". This figure has since been updated to €30m.

TABLE 14: ACHIEVEMENT OF RECOMMENDATIONS TO DATE – GERMANY[7]

ACHIEVEMENT OF RECOMMENDATIONS TO DATE	**JUSTIFICATION**
Recommendation 1: Recognise lifetime benefits	In economic evaluations: - Costs and benefits should be discounted at 3% after the first year. Identical constant rates of between 0% and 5% should be used in sensitivity analysis (IQWiG, 2022a). - The time horizon should be appropriate for the disease being considered. Time horizons greater than the average study length are preferred for chronic diseases, and costs and benefits must always be modelled over the same time horizon (IQWiG, 2022a).
Recommendation 2: Operationalise additional elements of value	In general (IQWiG, 2020): - Health outcomes of carers are considered if relevant. - Outcomes are prioritised by severity. Health impacts in more severe outcomes are considered to be of greater benefit. - Rare diseases: Orphan medicine products (OMPs) benefit from a simplified value assessment if the budget impact is <30 million euros annually (previously 50 million) (Koyencu and Herold, 2022).

[7] *It's important to note that when we refer to economic evaluation or cost-effectiveness analysis, most information is sourced from methodological guidelines and may not be reflective of routine practice.*

Recommendation 3: Develop standards for inclusion of RWE and surrogate endpoints	- Rare-disease treatments are assessed through the orphan medicines pathway by G-BA and are subject to more simplified evidentiary requirements (such as no need for comparative data) (Nicod et al., 2020). Surrogate Endpoints: - Surrogate endpoints need to be specifically accepted as valid. IQWiG provides guidance on the use of surrogate outcomes in their general methods guide (IQWiG, 2022a). - Their guidelines are considered the most "detailed and prescriptive European guidelines, providing suggestions of methods for the validation of surrogate outcomes. And defining necessary correlation levels for the association between surrogate and clinically relevant outcomes" (I.e. there is a cut-off for the acceptance of for the acceptance of surrogate outcomes) (Grigore et al., 2020). - IQWiG provides a detailed discussion on the potential use of surrogate outcomes in oncology (Grigore et al., 2020). Real-World Evidence (RWE): - For the initial assessment of clinical effect, there is typically an insistence on the use of head-to-head trials. - IQWiG supports the use of RWE to help assess predictive validity, which is a key factor in their validation of models (IQWiG, 2022a). Despite the guidelines set out above, local experience suggests that IQWiG and G-BA have a strong preference for RCT data and clinical endpoints and are likely only to accept RWE and surrogate endpoints when absolutely necessary.
Recommendation 4: Include outcome or other value-based arrangements	- Whilst there is no formal process for outcomes-based agreements, given that, in Germany, medicines are automatically reimbursed, the mandate of additional data collection will inform subsequent pricing adjustments. - Indeed, in 2019, Germany passed the GSAV law that gives the Federal Joint Committee increased authority to impose data collection requirements and price reductions if data do not support added value. However, this AbD process is rarely used (G-BA, 2022a). - While managed entry agreements are not commonplace in Germany, they have been used to support access to some gene therapies (including Kymriah® and Yescarta®) (Facey et al., 2021; Grubert, 2019). - Currently, there is a low level of digitisation in the health care sector which may be an important hurdle to the increased use of these types of agreements.
Recommendation 5: Expand data collection through registries and international collaboration	- The Medical Informatics Initiative (Medical Informatics Initiative Germany, 2023) aims to employ IT solutions to improve patient care and research through the aggregation and integration of health data. - The German Centre for Cancer Registry Data (ZfKD) pools and assesses data population-based cancer registries in each federal state. They publish statistics and evaluation findings on a regular basis, and the German Epidemiological Cancer Registries is available to scientists upon request (RKI, 2020). - G-BA has been involved in a pilot (EUnetHTA, 2020a) to assess the suitability of the ECFSPR and EBMT registry for CAR-T products for ALL, DLBCL, and PMBCL for post-launch evidence generation purposes in collaboration with a number of other agencies. However, in a recent report (IQWiG, 2022b), they considered that EBMT is not appropriate for German HTA purposes as a registry.

Recommendation 6: Enable early multi-stakeholder dialogue	- IQWiG and G-BA are part of EUnetHTA and engage with the Parallel EMA/EUnetHTA JSCs, which provides a single gateway for manufacturers to discuss their evidence generation plans (EUnetHTA, 2021a). Patients/patient representatives are also invited to participate in this process on a routine basis. However, only a limited number of JSCs are offered (EUnetHTA, 2021a). - As of September 2012, it is mandatory for companies seeking early advice from G-BA to do so in parallel with regulatory advice from Bundesinstitut fur Arzneimittel und Medi- ¨zinprodukte (BfArm) and Paul Ehrlich institute (PEI)(Cuche et al., 2014). Key areas for consultation include whether surrogate endpoint validation will meet IQWiG's criteria, choice of comparators and possible sub-group analysis.

4.7 Italy

HTA Agency: **Agenzia Italiana del Farmaco (AIFA)**

Main type of analysis: **Adopted cost-effectiveness analysis recently (previously used Therapeutic Added Value)**

TABLE 15: OUTCOMES OF HTA OF GENE THERAPIES - ITALY

GENE THERAPY (INTERNATIONAL NON-PROPRIETARY NAME OR INN)	GENE THERAPY (BRAND NAME)	HTA DECISION	ADDITIONAL COMMENTS
Talimogene Laherparepvec	Imlygic®	Not assessed	
Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	Strimvelis®	Recommended (Gozzo et al., 2021)	
Tisagenlecleucel	Kymriah®	Reimbursement with restriction	AIFA registry mandatory to select eligible patients and to monitor treatment response, even for the management of risk-sharing agreement (payment at result)(Gozzo et al., 2021)
Axicabtagene ciloleucel	Yescarta®	Reimbursement with restriction	AIFA registry mandatory to select eligible patients and to monitor treatment response, even for the management of risk-sharing agreement (payment at result)(Gozzo et al., 2021)
Voretigene neparvovec	Luxturna®	Reimbursement with restriction	AIFA registry mandatory to select eligible patients and to monitor treatment response (Gozzo et al., 2021)
Betibeglogene autotemcel	Zynteglo®	Not assessed	
Onasemnogene abeparvovec	Zolgensma®	Reimbursement with restriction	Patients weighing up to 13.5kg and clinical diagnosis of SMA type 1 and onset of symptoms during the first 6 months of life, or generic diagnosis of SMA type 1 (biallelic mutation in SMN1 gene and up to 2 copies of the SMN2 gene); AIFA registry mandatory to select eligible patients and to monitor treatment response, even for the management of risk-sharing agreement (payment at result)(Gozzo et al., 2021)
Autologous CD34+ cells encoding ARSA gene	Libmeldy®	Recommended (EVERSANA, 2021)	
Alipogene tiparvovec	Glybera®	Not assessed	

TABLE 16: ACHIEVEMENT OF RECOMMENDATIONS TO DATE - ITALY

ACHIEVEMENT OF RECOMMENDATIONS TO DATE	JUSTIFICATION
Recommendation 1: Recognise lifetime benefits	In economic evaluations: - Time horizon must be lifetime (or, in any case of a period long enough to capture all the differences between the alternatives compared) (AIFA, 2020a). - Base case discount rate of 3% for both costs and benefits. The discount rate can be varied in the analysis of univariate sensitivity (for example, from 0 to 5%) to evaluate the impact on the results of different assumptions on the discount rate (AIFA, 2020a).
Recommendation 2: Operationalise additional elements of value	In general (AIFA, 2018, 2020a): - Base case analysis must be provided from a national health system perspective. Additional assessment may be provided by the company with consideration of any direct health and non-health costs to be borne by the patient and/or society and indirect costs. - Medicines are classified by level of innovation (fully/ conditionally/non-) according to the level of therapeutic need, added therapeutic value, and quality of evidence available. - Severity and unmet need are also considered in the assessment of the level of innovation. - Other additional elements of value, such as equity and rarity, will not be considered in the economic evaluation.
Recommendation 3: Develop standards for inclusion of RWE and surrogate endpoints	Surrogate endpoints: - Scenario analysis that examines a spectrum of possible circumstances will be required when efficacy data are based on surrogate endpoints with an uncertain effect on final outcomes (AIFA, 2020a). - Added therapeutic value is graduated into five levels: maximum, important, moderate, poor, and absent. The definitions suggest that if surrogate outcomes are used, TAV is capped at moderate (AIFA, 2018, 2020a). This can also impact whether the product is considered innovative. The criteria for being considered an innovative product require the added therapeutic value to be judged as "maximum or important". If judged as moderate, the assessment of innovativeness will be considered on a case-by-case basis (AIFA, 2018). Real-World Evidence: - Real-world data can be used for the description of the patients for whom the product is intended (AIFA, 2020a). - Real-world data in Italy is requested for comparison with model outputs to validate models (AIFA, 2020a). - The guidelines for the inclusion of RWE and surrogate outcomes are limited.
Recommendation 4: Include outcome or other value-based arrangements	- Italy uses its long-established, national, web-based, treatment-specific data collection system linked to reimbursement (Facey et al., 2021). - Italian web-based registries commonly support patient-level outcome-based and economic risk-sharing agreements between manufacturers and AIFA, including for gene therapies. - Staged payment linked to individual patient outcomes have been used for tisagenlecleucel and axicabtagene ciloleucel

Recommendation 5: Expand data collection through registries and international collaboration	- However, in recent years the use of outcome-based payments has declined in favour of simpler confidential price discounts (Cole, Neri and Cookson, 2021). - AIFA monitoring registries are a national IT system where data on the use of products has been routinely collected since 2005 (AIFA, 2022). - For each monitored product, patients eligible for treatment are registered in the specific therapeutic indication dynamic monitoring database to collect epidemiologic and clinical data, including data on the safety profile, and ex-post information missing at the first evaluation stage (Montilla et al., 2015). - Through EUnetHTA, AIFA is leading a PLEG pilot to address remaining uncertainties and gather additional data on the use of Nusinersen® in patients with SMA. The pilot is being undertaken in collaboration with AAZ (Croatian Agency for Quality and Accreditation in Health and Social Welfare), FIMEA (Finnish Medicines Agency), INFARMED (Portuguese National Authority of Medicines and Health Products), NOMA (Norwegian Medicines Agency), ZIN. - AIFA is involved in a pilot (EUnetHTA, 2020a) to assess the suitability of the ECFSPR and the EBMT CAR-T products registry for ALL, DLBCL, and PMBCL for post-launch evidence generation purposes in collaboration with a number of other agencies.
Recommendation 6: Enable early multi-stakeholder dialogue	- National scientific advice by AIFA is temporarily suspended (AIFA, 2023) - including activities related to the Simultaneous National Scientific Advice (SNSA) pilot project (HMA, 2023) (a project designed to strengthen early regulatory support). - AIFA is a part of the EUnetHTA and engages with the Parallel EMA/EUnetHTA JSCs, which provides a single gateway for manufacturers to discuss their evidence generation plans. Patients/patient representatives are also invited to participate in this process on a routine basis. However, only a limited number of JSCs are offered (EUnetHTA, 2021a).

4.8 The Netherlands

HTA Agency: **Zorginstituut Nederland (ZIN)**

Main type of analysis: **Cost Effectiveness Analysis**

TABLE 17: OUTCOMES OF HTA OF GENE THERAPIES – THE NETHERLANDS

GENE THERAPY (INTERNATIONAL NON-PROPRIETARY NAME OR INN)	GENE THERAPY (BRAND NAME)	HTA DECISION	ADDITIONAL COMMENTS
Talimogene Laherparepvec	Imlygic®	Not assessed	
Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	Strimvelis®	Not assessed	
Tisagenlecleucel	Kymriah®	Recommended with restriction for ALL Recommended for DLBCL	Previously not recommended for DLBCL indication. Since June 2022, a financial arrangement has been agreed which will last until December 2024 and DLBCL is now recommended under this agreement. (ZiN, 2019b, 2022)
Axicabtagene ciloleucel	Yescarta®	Recommended (ZiN, 2019a)	
Voretigene neparvovec	Luxturna®	Recommended with restriction	Pay-for-performance agreement in place and discount to list price agreed. (ZiN, 2020)
Betibeglogene autotemcel	Zynteglo®	Recommended with restriction	Pay-for-performance agreement in place and discount to list price agreed (prior to withdrawal).(ZiN, 2021)
Onasemnogene abeparvovec	Zolgensma®	Recommended with restriction	Joint HTA and price negotiation with Belgium & Ireland (Beneluxa, 2021)
Autologous CD34+ cells encoding ARSA gene	Libmeldy®	Recommended but not Reimbursed	Positive HTA recommendation and price negotiations conducted with Belgium & Ireland. However, negotiations were unsuccessful as the manufacturer was not prepared to make the product available under the proposed reimbursement conditions. (Beneluxa, 2022; ZiN, 2023)
Alipogene tiparvovec	Glybera®	Not assessed	

TABLE 18: ACHIEVEMENT OF RECOMMENDATIONS TO DATE – THE NETHERLANDS

ACHIEVEMENT OF RECOMMENDATIONS TO DATE	JUSTIFICATION
Recommendation 1: Recognise lifetime benefits	- Unlike many other HTA bodies, ZIN has prescribed differential discounting since 2006 (4% for cost and 1.5% for effects), to account for the growing value of health benefits in the future (Versteegh, Knies and Brouwer, 2016; National Health Care Institute, 2016). - ZIN guidelines suggest conducting and reporting sensitivity analysis of the discount rate (National Health Care Institute, 2016). - ZIN also mandates the use of a lifetime perspective in modelling (National Health Care Institute, 2016).
Recommendation 2: Operationalise additional elements of value	- Since 2015, ZIN has linked disease severity ranges of 0.10 to 0.40, 0.41 to 0.70, and 0.71 to 1.00 with willingness-to-pay (WTP) reference values of €20 000, €50 000, and €80 000 per quality-adjusted life year gained, respectively (Schurer et al., 2022). These reference values are viewed more as the maximum WTP rather than fixed thresholds, i.e., the appraisal committee might deem a lower value more appropriate in certain circumstances. - In an update to their methods guidelines in 2016 (National Health Care Institute, 2016), ZIN suggested that, for the purpose of standardisation, the ICECAP (a measure of wellbeing) should be used in the case of *long-term and social care* alongside the EQ-5D (Versteegh, Knies and Brouwer, 2016). This suggests an awareness and openness to broader measures of health and wellbeing. However, this is not yet applicable to pharmaceuticals. - The monetary burden of carers is considered in base case cost-effectiveness analysis. Caregiver quality of life can be considered through scenario analysis - this was considered in the evaluation of Luxturna® (Huygens et al., 2021). - Pharmaceuticals that are designated as orphan medicine products by the EMA and have been approved for use by the EMA can be conditionally approved for inclusion in the basic health care package without HTA being required if the annual budget impact does not exceed €2.5 million (Ministerie van Volksgezondheid, 2020; Stafinski et al., 2022).
Recommendation 3: Develop standards for inclusion of RWE and surrogate endpoints	Surrogate endpoints: - According to Grigore et al. (2020), ZIN has surrogate outcome guidelines, which include examples of surrogate endpoints, acceptability criteria and provides an evidence strength assessment. Real-World Evidence: - According to Makady et al. (2017), ZIN will accept RWD to inform treatment effects under specific circumstances and accepts RWD to inform epidemiological data, resource use data and cost data. However, for the clinical assessment, all data must be published in a peer-reviewed manuscript for ZIN to consider it. - For rare diseases, there is a process that allows for more leniency around the quality of evidence (Nicod et al., 2020).
Recommendation 4: Include outcome or other value-based arrangements	- Outcome-based agreements can be considered for some orphan medicines or those with conditional or exceptional marketing authorizations and have been used, for example, for a 7-year outcomes-based managed entry agreement for Spinraza® (Facey et al., 2021).

	- These agreements are also possible for gene therapies, with pay for performance agreements recommended by ZIN for Luxturna®, Zynteglo® and Libmeldy®. However, as agreements with the Ministry of Health are strictly confidential, it is unknown whether these agreements have been implemented in practice. - The manufacturer of Zynteglo® included pay-for-performance options in their HTA submission to ZIN.
Recommendation 5: Expand data collection through registries and international collaboration	- ZIN is developing patient registries for the purpose of monitoring the use and (cost) effectiveness of expensive medicines. It also aims to link up with other similar initiatives (Ministerie van Volksgezondheid, 2019). However, this program is in a relatively early stage and, therefore, may not be beneficial for gene therapies coming to market in the immediate future. - Through EUnetHTA, ZIN is part of a PLEG pilot to address remaining uncertainties and gather additional data on the use of Spinraza in patients with Spinal muscular atrophy (EUnetHTA, 2020b). The pilot is being undertaken in collaboration with AAZ, FIMEA, INFARMED, NOMA and AIFA.
Recommendation 6: Enable early multi-stakeholder dialogue	- ZIN is a key stakeholder in EUnetHTA (leading the EUnetHTA 21 joint consortium) and provides early dialogue opportunities through EUnetHTA JSCs. However, a limited number of JSCs are currently conducted (EUnetHTA, 2021a), with timelines not necessarily aligned with the fast pace of development of gene therapies. - ZIN typically provides early advice on 6-10 products per year through EUnetHTA (Hanna and Toumi, 2020).

4.9 Spain

HTA Agency: La Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)[8]

Main type of analysis: Cost Effectiveness Analysis

TABLE 19: OUTCOMES OF HTA OF GENE THERAPIES- SPAIN

GENE THERAPY (INTERNATIONAL NON-PROPRIETARY NAME OR INN)	GENE THERAPY (BRAND NAME)	HTA DECISION	ADDITIONAL COMMENTS
Talimogene Laherparepvec	Imlygic®	Not recommended	Authorised but not marketed (AEMPS, 2023a)
Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	Strimvelis®	Not assessed	
Tisagenlecleucel	Kymriah®	Recommended with restriction	Payment by result, pharmacoclinic protocol and volume cap (for both indications*†) (Jørgensen, Hanna and Kefalas, 2020)
Axicabtagene ciloleucel	Yescarta®	Recommended with restriction	Payment by result, pharmacoclinic protocol and volume cap† (Jørgensen, Hanna and Kefalas, 2020)
Voretigene neparvovec	Luxturna®	Recommended with restriction	Pharmacoclinic protocol and volume cap†
Betibeglogene autotemcel	Zynteglo®	Not assessed	
Onasemnogene abeparvovec	Zolgensma®	Recommended with restriction	Payment by result & price-volume agreement (NAVLIN, 2021)
Autologous CD34+ cells encoding ARSA gene	Libmeldy®	Not recommended	Authorised but not marketed (AEMPS, 2023c)
Alipogene tiparvovec	Glybera®	Not recommended	Authorised but not marketed (AEMPS, 2023b)

*ALL: B-cell acute lymphoblastic leukaemia, DLBCL: Diffuse large B-cell lymphoma
†Pharmacoclinic protocol: Outline of the inclusion and exclusion criteria of suitable patients and general consideration for clinicians when using treatment. Volume cap: Prespecified maximum volume of medicine, which will be reimbursed by the payor.

[8] *AEMPS produces therapeutic positioning reports (Informe de Posicionamiento Terapeutico or IPTs) that typically assess the clinical effectiveness of new pharmaceuticals (Epstein and Espín, 2020). These AEMPS assessments inform pricing and reimbursement decisions, determining medicines that are to be included in the portfolio of 'common services' for which reimbursement is centrally approved by the Interministerial Committee on Pricing of Medicines and Healthcare Products (Comisión Interministerial de Precios de los Medicamentos, or CIPM) (Epstein and Espín, 2020). However, healthcare budgets in Spain are managed at the regional level, and a number of regions and hospital pharmacies conduct HTA from a clinical and economic perspective to inform their decision-making about restrictions and additions to the 'common portfolio' (EUnetHTA, 2017).*

TABLE 20: ACHIEVEMENT OF RECOMMENDATIONS TO DATE - SPAIN

ACHIEVEMENT OF RECOMMENDATIONS TO DATE	JUSTIFICATION
Recommendation 1: Recognise lifetime benefits	- We were able to identify the recommended discount rates for two regions of Spain. - In Catalonia, CatSalut recommend a base-case discount of 3% for costs and health effects, with a sensitivity analysis of 5% costs, 0 and 5% for health effects (Attema, Brouwer and Claxton, 2018). - In the Basque country, OSTEBA recommends a base-case discount rate of 5% for cost and health effects, with a sensitivity analysis of 0% for costs and 3% for health effects (Attema, Brouwer and Claxton, 2018). - No information was available regarding time horizons.
Recommendation 2: Operationalise additional elements of value	In general (see below for full criteria): - Severity considered through assessment of TAV. - Unmet need: Availability of other treatments considered in the assessment of TAV. - Equity: Effects on vulnerable subgroups of the population considered in TAV. According to current Spanish law (RDL 01/ 2015 art 92.1)(Real Decreto Legislativo 1/2015, de 24 de julio), the following criteria must be considered for the reimbursement of treatments: - a) **Severity**, duration and sequelae of the different pathologies for which the result indicated. - b) **Specific needs of certain groups**. - c) Therapeutic and social value of the medicine and its incremental clinical benefit considering its cost-effectiveness ratio. - d) Rationalization of public spending for pharmaceutical benefits and impact budget in the National Health System. - e) **Existence of medicines or other therapeutic alternatives** for their conditions at a lower price or lower cost of treatment. - f) Degree of innovation in the medicine Although the criterion of efficiency has been clearly reflected in Spanish laws and regulations for pricing and reimbursement at the national level for many years, its application at the national or regional level is still unknown (Oliva-Moreno et al., 2020).
Recommendation 3: Develop standards for inclusion of RWE and surrogate endpoints	Surrogate Endpoints: - The Galician Agency for Health Technology Assessment mentions surrogate endpoints in general terms but provides no specific methods or guidance on their use. - The Spanish Association of Health Technology Evaluation (AEETS) and the Andalusian Agency for Health Technology Assessment (AETSA) also have surrogate outcomes guidelines, but these were not deemed to provide detailed guidelines by Grigore et al. (2020). - The remaining regional HTA bodies have no surrogate outcomes guidelines (Agency of Health Quality and Assessment of Catalonia, General Directorate for Pharmacy and Medical Devices, Basque Office for Health Technology Assessment, SESCS). Real-World Evidence: - There is no evidence of guidelines on the generation and use of RWE.
Recommendation 4: Include outcome or	- In Spain, there is relatively little flexibility for RWE to inform payment at the national level (though this may be improving with the new

other value-based arrangements	establishment of a national registry), but more flexibility to implement risk-sharing agreements at the hospital- or regional-level (Cole, Neri and Cookson, 2021) - Outcome-based agreements have been implemented in Spain for some gene therapies, including Kymriah® (Facey et al., 2021). - However, it is worth noting that the "payment-at-result" contracts for the CAR-Ts were the first performance-linked reimbursement contracts to be agreed centrally in Spain ((Ronco et al., 2021).
Recommendation 5: Expand data collection through registries and international collaboration	- The Ministry of Health proposed the use of the new VALTERMED information system for the Spanish national health service to determine the therapeutic value in actual clinical practice. It is designed to collect real-world clinical data through a web-based tool to reduce the uncertainty associated with new therapies. Data was collected via the VALTERMED system to inform the outcomes-based payments of Kymriah®, Yescarta®, Zolgensma®, Alofisel® and Luxturna®. - Several autonomous regions have also developed their own registries, such as the Catalan registry, which is particularly well implemented and used by local hospitals. However, sharing data nationally can be difficult because the regional systems are not compatible. - AEMPS is involved in a pilot (EUnetHTA, 2020a) to assess the suitability of the ECFSPR for PLEG purposes in collaboration with a number of other agencies.
Recommendation 6: Enable early multi-stakeholder dialogue	- In 2018, the Spanish Ministry of Health approved the 'Plan for Approaching Advanced Therapies in the National Health System: CAR Medicines' aimed to organize the equitable, safe and efficient way to use CAR-T therapies (Zozaya et al., 2022). There is little indication of whether this plan is to be expanded to gene therapies in general. - AEMPS is a part of the EUnetHTA and engages with the Parallel EMA/EUnetHTA JSCS, which provides a single gateway for manufacturers to discuss their evidence generation plans. Patients/patient representatives are also invited to participate in this process on a routine basis. However, only a limited number of JSCs are offered (EUnetHTA, 2021a).

4.10 Sweden

HTA Agency: **Tandvårds- och läkemedelsförmånsverket (TLV) and Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU)**

Main type of analysis: **Cost Effectiveness Analysis**

TABLE 21: OUTCOMES OF HTA OF GENE THERAPIES - SWEDEN

GENE THERAPY (INTERNATIONAL NON-PROPRIETARY NAME OR INN)	GENE THERAPY (BRAND NAME)	HTA DECISION	ADDITIONAL COMMENTS
Talimogene Laherparepvec	Imlygic®	Not assessed	
Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	Strimvelis®	Not assessed	
Tisagenlecleucel	Kymriah®	Recommended with restriction for ALL	Recommended usage for patients up to 25 years of age with ALL who are R/R after transplantation/at second or subsequent recurrence (Eurordis, 2020)
		Not Recommended for DLBCL (Eurordis, 2020)	
Axicabtagene ciloleucel	Yescarta®	Reimbursement with restriction	Reimbursed for DLBCL and PMBCL after relapse or if the patient has not responded to treatment after two or more lines of treatment. Continual follow-up to address uncertainties recommended. (TLV, 2018)
Voretigene neparvovec	Luxturna®	Recommended (Janusinfo, 2022)	
Betibeglogene autotemcel	Zynteglo®	Assessed by Nordic collaboration FINOSE, No recommendation	
Onasemnogene abeparvovec	Zolgensma®	Reimbursement with restriction	Recommended for patients who weigh less than 13.5 kg and have up to 3 copies of the SMN 2 gene with SMA type 1 (NT Council, 2022)
Autologous CD34+ cells encoding ARSA gene	Libmeldy®	Assessed by Nordic collaboration FINOSE, No recommendation	
Alipogene tiparvovec	Glybera®	Not Assessed	

TABLE 22: ACHIEVEMENT OF RECOMMENDATIONS TO DATE - SWEDEN

ACHIEVEMENT OF RECOMMENDATIONS TO DATE	JUSTIFICATION
Recommendation 1: Recognise lifetime benefits	- TLV guidelines state that both costs and health effects should be discounted by 3%. They also recommend sensitivity analysis using 0% and 5% for both costs and health effects, as well as analysis where costs are discounted by 3% and health effects by 0% (TLV, 2003). - No information was found on the time horizon.
Recommendation 2: Operationalise additional elements of value	In general in assessments by the Swedish Agency for HTA (SBU, 2020): – Severity is considered through acceptance of an (implicit) higher cost-effectiveness threshold. – Equity can be considered qualitatively in appraisal through the principle of 'human value'. TLV is currently working on a paper on how to include or not include additional value drivers in their assessment process.
Recommendation 3: Develop standards for inclusion of RWE and surrogate endpoints	Surrogate Endpoints: – TLV and SBU have guidelines for the use of surrogate outcomes (Grigore et al., 2020). Real-World Evidence: – TLV was commissioned by the Swedish government to investigate the potential to develop follow-up using RWE, and this research is ongoing (TLV, 2020).
Recommendation 4: Include outcome or other value-based arrangements	- Sweden has a decentralised system where provinces/hospitals/councils negotiate pricing and reimbursement and any outcome-based agreements, but these are confidential. Due to the confidentiality of these agreements, the extent of their use isn't quantified. Additionally, there may be equity concerns due to the decentralisation of reimbursement decisions.
Recommendation 5: Expand data collection through registries and international collaboration	- TLV has made recommendations to the Swedish Government that national health data registries could be key to developing processes for the follow-up of medicines (TLV, 2021). Furthermore, TLV suggested that access to registries would be particularly relevant for innovative therapies. - Through EUnetHTA, TLV is leading a PLEG pilot to address remaining uncertainties and gather additional data on the use of Ibrance® in breast cancer patients. The pilot is being undertaken in collaboration with INFARMED, NIPN (National Institute on Pharmacy and Nutrition), NOMA and UCSC in an observatory capacity (Catholic University of the Sacred Heart, Italy). - TLV is involved in a pilot (EUnetHTA, 2020a) to assess the suitability of the ECFSPR cystic fibrosis registry and the EBMT CAR-T products (ALL), DLBCL and PMBCL registry for PLEG purposes in collaboration with a number of other agencies.

Recommendation 6: Enable early multi-stakeholder dialogue	- TLV is a part of the EUnetHTA and engages with the Parallel EMA/EUnetHTA JSCs, which provides a single gateway for manufacturers to discuss their evidence generation plans. Patients/patient representatives are also invited to participate in this process on a routine basis. However, only a limited number of JSCs are offered (EUnetHTA, 2021a). - Literature suggests that TLV may offer (or has previously piloted) offering early dialogue in partnership with the Medical Products Agency (MPA) (Cuche et al., 2014).

4.11 Switzerland

HTA Agency: **FOPH (Federal Office for Public Health)/BAG (Bundesamt für Gesundheit)**

Main type of analysis: The reimbursement of medicines is decreed by the FOPH following a submission for admission to a positive list (list of specialities or SL) by the market authorisation holder.[9]

TABLE 23: OUTCOMES OF HTA OF GENE THERAPIES - SWITZERLAND

GENE THERAPY (INTERNATIONAL NON-PROPRIETARY NAME OR INN)	GENE THERAPY (BRAND NAME)	ASSESSMENT DECISION	ADDITIONAL COMMENTS
Talimogene Laherparepvec	Imlygic®	Included on the List of Specialities (BAG, 2017)	
Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	Strimvelis®	Not included on the List of Specialties	
Tisagenlecleucel	Kymriah®	Not included on the List of Specialties	
Axicabtagene ciloleucel	Yescarta®	Not included on the List of Specialties	
Voretigene neparvovec	Luxturna®	Included on the List of Specialities (BAG, 2021)	
Betibeglogene autotemcel	Zynteglo®	Not included on the List of Specialties	
Onasemnogene abeparvovec	Zolgensma®	Included on the List of Specialities	Included on the list of specialities for congenital defects (Geburtsgebrechen-Spezialitätenliste/GG-SL), a reimbursement pathway for medicines for rare birth defects. (Stettner et al., 2023)
Autologous CD34+ cells encoding ARSA gene	Libmeldy®	Not included on the List of Specialties	
Alipogene tiparvovec	Glybera®	Not included on the List of Specialties	

[9] *HTA is not routinely conducted nor is it a mandatory part of the reimbursement process. In some topics (determined by the Federal Medical Services Commission (ELGK) and the Federal Medicines Commission (EAK), a type of HTA is carried out by an external partner (usually an academic group) and then presented to the FOPH. FOPH then makes a decisions to continue, restrict or terminate reimbursement.*
Medicinal Products on the SL are considered compulsory medicinal products and are reimbursed as part of the compulsory health insurance (OKP) (BAG, 2022a).

TABLE 24: ACHIEVEMENT OF RECOMMENDATIONS TO DATE - SWITZERLAND

ACHIEVEMENT OF RECOMMENDATIONS TO DATE	JUSTIFICATION
Recommendation 1: Recognise lifetime benefits	- There are no guidelines or assessment reports that enable us to determine the extent to which the lifetime benefits are considered in assessments.
Recommendation 2: Operationalise additional elements of value	- Up until January 2021, Switzerland automatically granted reimbursement for diseases included in the national list of birth defects and congenital disorders (Nicod et al., 2020). However, there has since been a change in the law, which now requires medicines for birth defects to be assessed by the same body and process as all other medicines. - Additionally, we found no evidence of other additional elements of value being considered.
Recommendation 3: Develop standards for inclusion of RWE and surrogate endpoints	Surrogate Endpoints: - The FOPH has no guidelines for the use of surrogate outcomes (Grigore et al., 2020). Real-World Evidence: - There are no guidelines to establish how and when to incorporate real-world evidence (RWE) in assessments.
Recommendation 4: Include outcome or other value-based arrangements	- Three types of managed entry agreements are being used in Switzerland: price refunds, sales volume limits, and pay-for-performance (or outcomes-based agreements) (EVERSANA, 2020b) - An outcomes-based agreement is in place for Zolgensma® (BAG, 2022b). If there is a lack of therapeutic benefit identified by four pre-specified conditions[10], then the manufacturer (Novartis) must reimburse the payer. - The introduction of these agreements can help to manage uncertainty, but the inclusion of these agreements as part of the decision to reimburse is relatively new, and so their effectiveness in Switzerland is still to be determined.
Recommendation 5: Expand data collection through registries and international collaboration	- Switzerland has experience in using financial incentives to enhance comprehensive reporting in registries through reimbursement of transplants being conditional on reporting to the Swiss registry and adherence to a specific quality management system (Stampf et al., 2021). - Physicians have an obligation to record data for those treated with Zolgensma® in the Swiss register for neuromuscular diseases (BAG, 2022b). - Other national registries include the Swiss Rare Disease Registry

[10] The following criteria (BAG, 2022b) define a lack of therapeutic benefit, which triggers a reimbursement obligation by Novartis Pharma Switzerland:
1) death due to worsening of the SMA; or
2) patients who are newly on invasive continuous ventilation (16 or more hours per day for 21 consecutive days) with no acute reversible infection, as documented by CHOP code (Swiss Classification of Surgical Interventions) during inpatient treatment; or
3) the need for a permanent tracheostomy, with simultaneous deterioration of motor functions according to scores of one of the motor systems listed below; or
4) overall deterioration of motor function in 2 different motor scores (except for severely impaired patients where only 1 criterion is required, CHOP-INTEND), confirmed by 2 consecutive measurements, without an alternative justification for the deterioration.

Motor function scores:
1. *patients under 2 years of age: CHOP-INTEND (> 4 points); RULM (> 3 points)*
2. *Patients aged at least 2 years: HFMSE (> 3 points); RULM (> 3 points)*

(CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE = Hammersmith Functional Motor Scale Expanded; RULM = Revised Upper limb Module)

	(SRDR). The registry description indicates that they foresee international collaboration in the future. - Switzerland has several established national-level registries that will enable a greater understanding of patients and diseases in Switzerland and provide infrastructure for post-approval evidence generation to address uncertainties. - Greater international collaboration would be beneficial.
Recommendation 6: Enable early multi-stakeholder dialogue	- We are unable to find evidence of early multi-stakeholder dialogue.

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