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Systematic Literature Review

A Review of Methodological Considerations for Economic Evaluations of Gene Therapies and Their Application in Literature



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ABSTRACT

Objectives: To identify methodological considerations discussed in literature addressing economic evaluations (EEs) of gene therapies (GTs). Additionally, we assessed if these considerations are applied in published GT EEs to increase understanding and explore impact.

Methods: First a peer-reviewed literature review was performed to identify research addressing methodological considerations of GT EEs until August 2019. Identified considerations were grouped in themes using thematic content analysis. A second literature search was conducted in which we identified published evaluations. The EE quality of reporting was assessed using Consolidated Health Economic Evaluation Reporting Standards.

Results: The first literature search yielded 13 articles discussing methodological considerations. The second search provided 12 EEs. Considerations identified were payment models, definition of perspectives, addressing uncertainty, data extrapolation, discount rates, novel value elements, and use of indirect and surrogate endpoints. All EEs scored satisfactory to good according to Consolidated Health Economic Evaluation Reporting Standards. Regarding methodological application, we found 1 methodological element (payment models) was applied in 2 base cases. Scenarios explored alternative perspectives, survival assumptions, and extrapolation methods in 10 EEs.

Conclusions: Although EE quality of reporting was considered good, their informativeness for health technology assessment and decision makers seemed limited owing to many uncertainties. We suggest accepted EE methods can broadly be applied to GTs, but few elements may need adjustment. Further research and multi-stakeholder consensus is needed to determine appropriateness and application of individual methodological considerations. For now, we recommend including scenario analyses to explore impact of methodological choices and (clinical) uncertainties. This study contributes to better understanding of perceived appropriate evaluation of GTs and informs best modeling practices.

Keywords: gene therapy, economic evaluations, methods, methodological considerations, applications.

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Introduction

Recent advances in biomedical research resulted in the introduction of gene therapies (GTs) to clinical practice.¹ GTs have the potential to provide significant long-term benefits for conditions that currently have no or few treatment options. Pharmaceutical development forecasts show over a dozen GTs are expected to apply for market authorization in the next few years.² Despite a steady increase in market authorizations, widespread reimbursement and patient access is not yet observed.³ Up-front high prices combined with long-term value claims supported by little clinical evidence raise concerns for reimbursement and affordability by health technology assessment (HTA) authorities and payers.^{4,5}

GTs are said to have specific characteristics, suggesting traditional HTA should be adapted, in particular the economic evaluations (EEs).⁶ In anticipation of the first ex-vivo chimeric antigen receptor T-cell (CAR-T) receiving central marketing authorization (MA), the National Institute for Health and Care Excellence (NICE) proactively issued a mock appraisal of an exemplar CAR-T therapy.⁷ This mock appraisal concluded that overall, NICE's existing technical appraisal methods and decision framework is applicable to GTs. But specific elements need adjustment to integrally appraise the uncertainty of their long-term cost and benefit.⁷ These elements were introduction of risk sharing via innovative payment schemes, quantification of decision uncertainty, and choice of discount rate.⁷ Since publication of the NICE mock appraisal, more methodological elements

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for incorporation in the economical evaluations of GTs were discussed in literature.^{6,8-13}

The importance of EEs in healthcare decision making is well recognized.¹⁴ Although individual jurisdictions might weigh the results of the evaluations differently, the requirement by authorities to include EEs in assessments is increasing. Nevertheless, with the introduction of GTs, the question is raised whether accepted good modeling practices are suited to assess and value these novel therapies.^{6,8} With the expected influx of GTs, early identification and adjustment of appropriate methodology is essential.

An increasing number of perspective and commentary-style articles explore and discuss specific elements of EEs that warrant adjustment when modeling GTs.^{6,11,15,16} Work by Jørgenson et al. is the first to explore the impact of a specific methodological element by modeling the budget impact of an annuity payment model compared to a traditional one-off payment in a hypothetical high-value treatment.¹⁷ This first impact quantification of a novel payment model proves to be insightful and may inform authorities to design payment schemes, yet it remains a hypothetical scenario. Additionally, 1 systematic review was identified of CAR-T EEs indicated for acute lymphoblastic leukemia.¹⁸ Although informative, this article included a specific type of GT EEs for 1 single indication and adheres to traditional EE practices. So far, no timely overview has been made of methodological elements discussed in literature specifically relating to EEs for curative GTs. Nor has their application and impact been explored in EEs of GTs published in literature.

Therefore, the primary objective of this research is to identify methodological considerations discussed in literature specifically addressing EEs for GTs. Next, we will assess if these methodological elements are applied in published GT EE studies to increase understanding of these methods and their impact. This study will contribute to a better understanding of discussions regarding appropriate evaluation of costs and benefits of GTs and inform best modeling practices.

Methods

Study Design

We conducted a literature review with the primary aim to identify peer-reviewed papers addressing methodological considerations, specifically addressing EEs of GTs, published between January 2007 and August 2019. January 2007 was chosen because this is the year in which the European Advanced Therapy Medicinal Product regulation was invoked.¹⁹ This regulation was the first to formally define GTs as a medicinal product.¹⁹ The secondary aim was to identify EEs of GTs in the same time frame. GTs in this research are defined as products that are one-off administered or have a short-term treatment course, with the intention to achieve substantial sustained or curative effect.²⁰ This definition includes both in-vivo and ex-vivo GTs.¹⁹ GT EEs were included if the products were intended to or authorized by a private authorization holder. This excludes GTs developed in hospitals or primarily in an academic setting, as well as products applied under managed access programs (eg, named patient use, compassionate use, hospital exemption schemes) that do not intend to formally apply for market authorization.

Search Strategy and Study Selection

To identify studies addressing methodological considerations as well as EEs for GTs, we conducted a systematic search of

MEDLINE, Embase, PubMed, Cochrane, Database of Abstracts and reviews of Effects, National Healthcare Service Economic Evaluation Database, and Tufts Cost-Effectiveness Analysis Registry We used the following (shortened) search query in all databases: (“economic evaluation”[MeSH] AND “gene therapy” [all items]).

An additional manual snowball search was done, in which references of included studies were reviewed. We conducted another manual search of each database using “economic evaluation”[MESH] combined with brand and generic names of GT products that applied for initial European Medicines Agency and US Food and Drug Administration market authorization to date (August 2019).² Broad search terms were deliberately used to identify all scientific literature addressing GTs, methodological considerations, and EEs.

Research discussing methodological considerations included commentaries, perspectives, editorials, or invited contributions (hereafter called commentaries) and were required to identify 1 or more challenges as well as propose solutions. Commentaries only discussing affordability challenges or cost without proposing solutions were excluded.

Eligible EEs had to report both effectiveness and cost outcomes such as cost-utility analyses, cost-effectiveness analyses, and early economic analyses. Studies reporting only effectiveness data—such as clinical trials, patient-reported outcomes, or quality-of-life data—or only cost findings—such as cost-minimization analyses, cost-benefit analyses, burden of disease, or cost of illness—were excluded. EEs were required to be primary research excluding National Institute of Health Research technology appraisals or systematic reviews.

Both commentaries and EEs had to be written in English with access to full articles. Conference abstracts were excluded as well as EEs of fictive treatments. Articles addressing genetic tests, genotyping, and whole genome sequencing interventions were also excluded. Both the literature search and eligibility assessment of identified literature was performed independently by 2 researchers (R.t.H. and G.F.). Results were compared and discrepancies were discussed until consensus was reached.

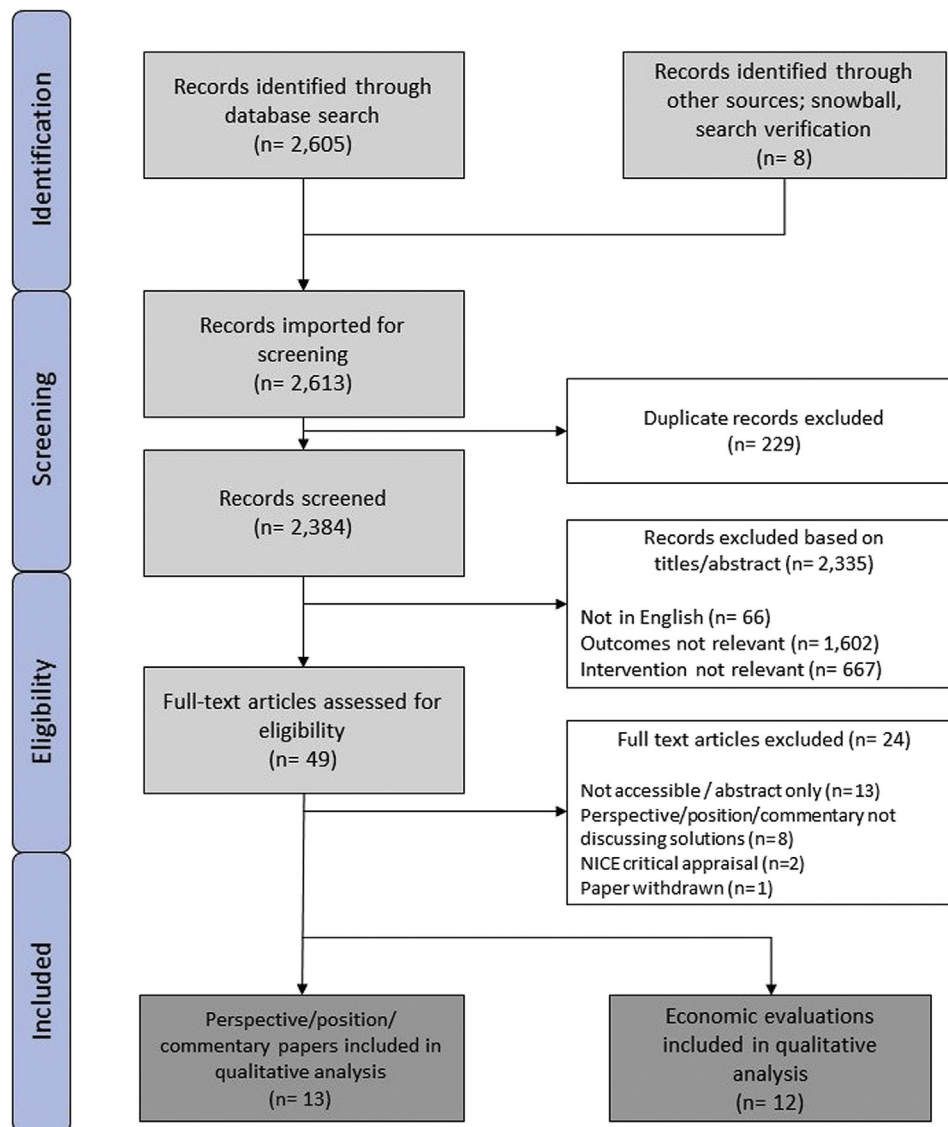
Data Extraction and Quality Assessment

Methodological considerations were extracted from included commentaries using a predefined data extraction form. Data extraction was done independently by 2 researchers (R.t.H. and G.F.). Discrepancies were discussed until consensus was reached. Considerations were grouped into themes using thematic content analysis methods.²¹

Study characteristics of included EEs were collected using a predefined data extraction form. The quality of EE reporting was assessed using Consolidated Health Economic Evaluation Reporting Standards (CHEERS).²² The CHEERS checklist was again scored independently by 2 researchers (R.t.H. and G.F.). Scoring discrepancies were discussed until consensus was reached. Last, a descriptive analysis was performed comparing methodological elements identified in commentaries and their application in published EEs.

Results

In total, 2613 records were identified, 2605 via the database search and 8 through manual and snowball search. Results of the search are presented in Figure 1 in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.²³ After identification, 229 duplicate records were removed. Screening of titles

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

NICE indicates National Institute for Health and Care Excellence.

and abstracts led to exclusion of 2335 studies for not being in English ($n = 66$), irrelevant outcomes ($n = 1602$) meaning not including both cost and effect, or irrelevant interventions ($n = 667$) meaning not a GT. Detailed screening of full articles led to exclusion of 24 more records for reasons further specified in Figure 1.

The first literature search yielded 13 commentaries. Data extraction provided 61 considerations, which were grouped into 7 themes.²¹ Themes and associated considerations are presented in Table 1. Themes were defined to be mutually exclusive. Grouping of the 61 extracted methodological elements led to 41 unique considerations.

The second literature search yielded 12 EEs. Study characteristics are presented in Table 2. These EEs reported 8 different GTs intended for 8 distinct indications. Of these indications, 5 were oncologic: prostate cancer, acute lymphoblastic leukemia (2x), diffuse lymphoma, and metastatic melanoma.²⁴⁻³⁰ Other indications were hemophilia A, β -thalassemia, spinal muscular

atrophy, and inherited retinal disease.³¹⁻³⁵ The MA of the GT-indicated product for prostate cancer (sipuleucel-T) was withdrawn from the EU market by the MA holder at time of our search. The hemophilia A (AAV5-hFVIII-SQ) and β -thalassemia (no generic or brand name reported) products did not yet file for MA in the United States or Europe, but a secondary search confirmed the developers intend to do so. Products reported in the remaining 9 EEs currently have active MAs in both the United States and/or Europe.^{24-30,33-35}

Three studies (25%) reported use of the CHEERS checklist.^{24,29,30} Of these studies, 2 authored by the same group, also incorporated recommendations of the Second Panel on Cost-Effectiveness in Health and Medicines.^{24,30,36} One study (8%) reported validation via the panel's recommendations alone.²⁶ Eight studies (67%) did not report use of a quality or validation tool.^{25,27,28,32-35} We assessed the quality of reporting of all included EEs with the CHEERS checklist. The populated CHEERS

Table 1. Methodological considerations discussed in literature to properly value both benefits and cost of curative GTs in economic evaluations.

Theme	Considerations	Source
 <p>Payment models</p>	<p>Performance-based contract (including milestone based contract, value-based contract, pay-for-performance scheme, performance-based risk-sharing arrangements, outcome-based agreements, outcome-based contracts, performance-linked, value-based agreement reimbursement)</p> <p>Annuity payment (including installment payments)</p> <p>Value-based pricing</p> <p>Leased payments</p> <p>Amortization</p> <p>Reinsurance market</p> <p>Managed entry agreement</p> <p>Intellectual property-based payment</p> <p>Fund-based payment</p> <p>Rate of return pricing</p> <p>Total cost of care</p> <p>Capitation</p> <p>Shared savings</p>	<p>6,8,9,11,15,16,37</p> <p>8,9,11,16</p> <p>6,37</p> <p>15,16</p> <p>15,16</p> <p>8</p> <p>37</p> <p>37</p> <p>37</p> <p>10</p> <p>13</p> <p>13</p> <p>13</p>
 <p>(Re)definition of perspectives</p>	<p>Besides the impact on patient quality of life, aspects with a greater economic impact on the society should be included.</p> <p>Inclusion of wider personal, social, and economic benefits besides treatment cost only</p> <p>Structural inclusion of 2 reference cases: one with a societal perspective and the other with a healthcare sector perspective</p> <p>Inclusion of an impact inventory to address that GTs can have important non-health consequences such as effects on family caregivers, education costs, and economic productivity</p> <p>Inclusion of infrastructure and capital cost to administer these drugs to reflect not all patients have access to specialized treatment centers</p>	<p>6,13</p> <p>37</p> <p>6</p> <p>6</p> <p>14</p>
 <p>Addressing uncertainty</p>	<p>Consideration of (routine) use of expected value of information</p> <p>Inclusion of other complementary nonrandomized data, for example, natural history data, registries, utility data, and the use of pooled data</p> <p>Inclusion of (probabilistic) sensitivity analyses to characterize and quantify decision uncertainty</p> <p>Inclusion of net health effects as outcome to provide information on the size of the uncertainty</p> <p>There is a need for more sophisticated methods that reduce decision uncertainty in EEs</p>	<p>6,15</p> <p>15,37</p> <p>14</p> <p>16</p> <p>14</p>
 <p>Data extrapolation</p>	<p>Structural incorporation of the potential for patients to discontinue treatment owing to any reason, including failure of manufacturing process</p> <p>Inclusion of analyses using different time horizons relating different levels of certainty about treatment effect or scenarios to address the current available short-term evidence that extrapolated to simulate long-term benefits</p> <p>Inclusion of adverse health effects that may be irreversible in the case of a one-off cure</p> <p>Parametric methods may underestimate survival, primarily when a plateau of long-term survival is observed. A mixed cure model allows incorporation of cured and non-cured patients.</p> <p>Partitioned survival models are often used for the EE oncology treatments; this modeling approach often seems to fail to properly incorporate the complexity of the disease and novel technologies.</p>	<p>14,16</p> <p>6</p> <p>16</p> <p>15</p> <p>14</p>

continued on next page

Table 1. Continued



Theme	Considerations	Source
	<p>Sensitivity analysis should routinely include use of discount rates of 0% to 5%</p> <p>The practice of using the same discount rate for both costs and benefits is questioned for curative therapies. Use of a lower discount rate would increase the relative size of the irreversibility, because long-term effects will have a higher present value.</p> <p>Exploration of differential discounting whereby health benefits are discounted at a typically lower rate than costs, and variable discounting whereby the rate is altered over time.</p> <p>Discount rates on health effects should be 1%-3.5% lower than the discount rate applied to costs.</p>	<p>6,15</p> <p>6</p> <p>16</p> <p>15</p> <p>15</p>
Discount rates		
	<p>Broadening the definition of “value” to capture elements of value not captured in the QALY, considering the value of ATMPs and the value forgone in other disease areas.</p> <p>Severity of disease should be considered.</p> <p>To comprehensively capture the value of (high investment) medications, novel value assessment methodologies, such as multiple criteria decision analysis, may need to be applied.</p> <p>The following aspects are currently not adequately captured in calculations of QALYs: valuation of cure as opposed to wider incremental benefits, social value beyond health gain, patient preferences for treatments beyond health gain, process utilities, option value, and value of spillovers linked to innovation.</p> <p>Novel elements of value can be relevant for GTs and are worthy of consideration: scientific spillover, equity, real option value, value of hope, severity of disease, insurance value, fear of contagion, and reduction in uncertainty.</p> <p>There is a need for new methods that more accurately capture the value of new innovative drugs that might include treatment to cure for some fraction of the treated patients</p>	<p>15</p> <p>11</p> <p>8</p> <p>15</p> <p>6</p> <p>15</p>
Novel value elements		
	<p>The primary endpoint of GT EEs are often surrogate endpoints. This raises questions about their validity and predictability, especially in rare, poorly studied conditions. Ideally, the value of the standard of care has been identified and quantified for use in new treatment comparisons.</p> <p>Use of a surrogate endpoint is sometimes unavoidable. Therefore, it is important to know whether any attempts have been made to evaluate and validate them.</p> <p>GTs often fulfill a previously unmet need and therefore there is no existing therapy to be replaced. This may generate cost offsets.</p> <p>Historical cohorts may be acceptable when the population is relatively homogeneous, when confounding factors are well known, when patient management is established and standardized, when the primary endpoint is objective and robust, and when the effect size of the new therapy is substantial versus the historical cohort.</p>	<p>6,8</p> <p>6</p> <p>10</p> <p>6</p>
Use of indirect comparisons and surrogate endpoints		

table is included as a supplemental table (see [Appendix Table 1 in Supplemental Materials](#) found at <https://doi.org/10.1016/j.jval.2020.04.1833>). Based on [Appendix Table 1](#), we find that the quality of reporting of the included EEs ranges from enough to good.

Below, a descriptive analysis is given of the identified methodological considerations per theme and how they may be incorporated in EEs.

Payment Models

Payment and billing in healthcare systems is generally organized to occur at the same time treatment is provided.^{11,13} For chronic treatments this results in a longitudinal and predictable spending pattern, which allows payers to plan budgets and spending.³⁷ Additionally, if a treatment is deemed ineffective, a treatment can be stopped, and payment is discontinued. In the case of curative GTs, the treatment is administered in the present time, as is payment, while the effect is to be benefitted from in the future. These so-called up-front payments are found to be substantial for the products currently on the market, while the long-term effectiveness is uncertain and often not clinically confirmed.² Also, if a GT proves to be less effective than claimed, the treatment cannot be stopped, nor can the cost be recouped. Alternative payment models are often mentioned in the context of GTs and affordability as a measure to decrease budget impact and spread payment over more multiple financial years.

Main arguments in favor of these alternative payment models given in the commentaries are risk-sharing between the payer and manufacturer and spreading cost by allowing payers to make installment payments over an extended period.⁸ This was said to be driven by the way health systems are organized as well as addressing affordability concerns.¹⁰ Current reimbursement models rely on up-front payments.³⁷ Therefore, implementation of alternative payment models would require structural changes and significant administrative preparations.¹¹ The commentaries propose 13 different payment models for curative GTs ([Table 1](#)). Of these payment models, performance-based contracts (albeit using different names, eg, pay-for-performance schemes, milestone-based contract) and annuity payments were mentioned most. Performance-based contracts are said to be preferred over annuity payments in situations with high budget impact and considerable uncertainty in the evidence base.¹⁵ The key to success with these contracts is described to be collection of relevant and unbiased data.¹⁵ Other models mentioned are value-based pricing (VBP), leased payments, amortization, reinsurance market, intellectual property-based payment, fund-based payment, rate of return pricing, total cost of care, capitation, and shared saving managed entry agreements ([Table 1](#)).

In the included EEs, 2 outcome-based payment models were modeled (17%).^{26,33} The remaining 10 studies (83%) mention no specific payment scheme, in which we assumed a classic one-off payment model is applied ([Table 1](#)). An outcome-based payment model is evaluated by Whittington et al and entails payment after treatment response 1 month post-treatment.²⁶ After initial introduction of the payment model, the authors do not discuss the implications of this choice. Malone et al describes a similar scheme, defined as payment after a 3-month response.³³ Like Whittington, the authors do not further discuss the impact of their choice.

(Re)definition of Perspectives

With the translation of GTs to the clinic, new treatment options might become available for indications previously deemed incurable.³⁸ With these new opportunities, new cost elements are

introduced, expanded, or diminished.¹¹ More common elements such as introduction of (cured) individuals to the workforce could become impactful, while informal care may decrease. Also, new cost elements are introduced, which are associated with the unique GT supply chain and specialized care.³⁹

Redefinition of value elements recently has been discussed more broadly in the health economics field.⁴⁰ Considerations discussed in the commentaries included in this theme include structural inclusion of wider cost items such as social care, effects on family and caregivers, (healthcare worker) education costs, and economic productivity.⁶ Authors reason that GTs address high-burden disease, which also affects relatives and caregivers.^{6,13,37} Treatment with GTs may result in (re)introduction of these patients and their caregivers to the workforce, which could generate tax income and (informal) care savings. Drummond et al and Ettinger et al propose structural inclusion of these costs to reflect this greater economic impact.^{6,13} Carr et al advocates to, besides cost of treatment, also include personal, social, and economic benefits but does not specify what exactly this entails.³⁷ Raymakers et al takes it a step further and proposes inclusion of infrastructure and capital cost in evaluations.¹⁴ He reasons not all patients have direct access to the specialized treatment centers that are often required to administer these therapies.¹⁴ Last, Drummond et al proposes structural inclusion of 2 reference cases into evaluations: 1 base case using a societal perspective and 1 from a healthcare sector perspective.⁶ This same commentary proposes an *impact inventory* that incorporates non-health consequences such as education cost, effect on family caregivers, and productivity.⁶ The suggestion to implement 2 reference cases and an impact inventory is adopted from recommendations by the Second Panel on Cost-Effectiveness in Health and Medicine.³⁶

The primary perspective applied in EEs was the payer perspective ($n = 7$, 58%),^{26,27,29,30,31,33} of which 3 studies further specified their perspective as a public payer,²⁹ commercial insurer,³³ and healthcare payer perspective.³⁰ Three studies (25%) used a healthcare perspective.^{31,32,34} Gong et al was the only research to take a societal perspective in a US setting (8%), which is uncommon.²⁵ A rationale for this choice was not given. One (8%) study did not report which perspective was applied but observing direct medical and indirect nonmedical were included, we assume a modified societal perspective was used.³⁵ Two studies explored an alternative perspective in a scenario^{29,32}: Whittington et al²⁹ explored a commercial payer and public payer perspective, the difference being inclusion of hospital markup cost for treatment acquisition in the private scenario. This resulted in an estimated incremental cost-effectiveness ratio (ICER) of \$896 600 per QALY for public payers and \$1 615 000 per QALY for commercial payers, showing considerable impact. In line with the considerations of the Second Panel and Drummond et al is the additional societal scenario to the base-case healthcare perspective evaluated in Coquerelle et al.³² The societal scenario here only takes productivity losses into account.³² This EE shows the impact of productivity loss inclusion on 2-year treatment cost, which was higher in the hematopoietic stem cell transplantation comparator group (€13 971/patient) than in the GT intervention group (€7545/patient). Nevertheless, the societal perspective applied in this study does not comply with the formal societal perspective definition in literature⁴¹ and authority guidelines.⁴²

Addressing Uncertainty

Occurrence of uncertainty in EEs is a given and to a certain extent accepted.^{43,44} Yet, in the context of GTs it seems more uncertainty is perceived.¹⁴ This may partially be attributed to

Table 2. Characteristics of gene therapy economic evaluations published in peer-reviewed literature until August 2019. Studies listed in order of publication year.

	Gong et al ²⁵	Machin et al ³¹	Lin et al ²⁴	Whittington et al (2018) ²⁶ (Kymriah)	Roth et al ²⁷	Almutairu et al ²⁸	Zimmermann et al ³⁴	Whittington et al (2019) ²⁹	Malone et al ³³	Lin & Muffly et al ³⁰	Coquerelle et al ³²	Johnson et al ³⁵
General												
Base case population	Pre-docetaxel asymptomatic mCRC with no prior chemotherapy	30- to 40-year-old male patients with uncomplicated severe hemophilia A	Patients <25 years with B-cell acute lymphoblastic leukemia that is refractory or in second or later relapse	Patients <25 years with B-cell acute lymphoblastic leukemia that is refractory or in second or later relapse	Adults with relapsed/refractory large DLBCL	Histologically confirmed stage IIIB- IVM1c malignant unresectable melanoma	Biallelic RPE-mediated inherited retinal disease	Adults with relapsed/refractory large DLBCL	Infants with genetically confirmed SMA1, 2, copies of SMN2, diagnosed <6 months	Adults with relapsed/refractory large DLBCL	Major β-thalassemia	Biallelic RPE-mediated inherited retinal disease
Geography	US	US	US	US	US	US	US	US	US	US	France	US
Study design	Cost utility analysis	Cost utility analysis	Cost utility analysis	Cost utility analysis	Cost utility analysis	Cost utility analysis	Cost utility analysis	Cost utility analysis	Cost utility analysis	Cost utility analysis	monocentric retrospective comparative microcosting and CEA	Cost utility analysis
Intervention (gene therapy)	Provenga (sipuleucel-T)	AAV5-hFVIII-SQ	Kymriah (tisagenlecleucel)	Kymriah (tisagenlecleucel)	Yescarta (axicabtagene ciloleucel)	Imlygic (talimogene Laherparepvec) and ipilimumab	Luxturna (voretigene neparovvec)	Yescarta (axicabtagene ciloleucel)	Zolgensma (onasemnogene abeparvovec-xioi)	Yescarta (axicabtagene ciloleucel [A]) Kymriah (tisagenlecleucel [T])	NR	Luxturna (voretigene neparovvec-ryl)
Comparator(s)	Abiraterone (ABI), prednisone (Pred)	Prophylactic factor VIII	Blinatumomab	Clofarabine	Salvage chemotherapy (R-DHAP)	Ipilimumab	Regular physician visits and supportive care	Salvage chemotherapy R-DHAP	Nusinersen with non-disease best supportive care	Salvage chemotherapy	HSCT	Psychological support and visual rehabilitation
Model												
Model structure	Markov Model	Markov model	Markov model	Decision tree followed by Markov model	Decision tree followed by Markov model	Markov	Markov structure	Decision tree followed by Markov model	Markov model	Markov model	NA	Markov model
Time horizon	Life time	10 years	Life time	Life time	Life time	Life time	Lifetime	Lifetime	Lifetime horizon	Lifetime	2 years	Lifetime
Perspective	Societal perspective	third party healthcare perspective	Payer perspective	Payer perspective	Payer perspective	Payer perspective	Healthcare perspective	Public payer perspective	Commercial insurer perspective	Healthcare payer perspective	Healthcare perspective	NR
Cycle length	Monthly	Monthly	Monthly	NR	Monthly	NR	1 year	Monthly	6 months (first 3 years), then yearly	Monthly	NR	NR
Effect measure and unit	LYs, QALYs, cost, ACER, ICER	QALYs, cost, ICER	LYs, QALYs, cost, ICER	LYs, QALYs, cost, ICER	LYs, QALYs, costs, ICER	PF-LY, PF-QALYs, ORR, ICER, PF-ICUR	Visual acuity (VA), PF-visual field (VF), QALYs, cost, ICER	LYs, QALYs, cost, ICER	LYs, QALYs, cost, ICER	LYs, QALYs, cost, ICER	2-year survival without major cost, complications	QALY, ICER
Input parameters												
Clinical data	3-year trial data	2-year trial data and 10-year animal data	13-month trial data	18.6-month trial data	1-year trial data	3-year trial data	2-year trial data and 7-year anecdotal follow-up	2-year trial data	2-year clinical trial	A: 27 months T: 14 months	2-year follow-up	1.5-year trial
Utility data	Secondary literature	Literature and clinician estimates	Secondary literature	NR	EQ-5D-5L with US tariffs alongside clinical trial	Secondary literature	Mapping study	Literature	CHERISH trial	lymphoma literature	NA	Literature and expert opinion
Data extrapolation	DEALE method	NR	Model calibration	Weibull, exponential, log-normal, log-logistic, Gompertz	Weibull, log-log, log-logistic, Gompertz	Weibull	Exponential	Standard parametric, flexible parametric, 2 mixture cure models, flexible parametric mixture model	Exponential, log-normal, log-logistic, Weibull, generalized gamma, Gompertz	Piecewise exponential function	NA	Exponential, Weibull, Gompertz, loglogistic, lognormal, generalized gamma
Scenarios	NR	NR	1: 5-year PFS 20% 2: 5-year PFS 0% 3: Bridge to transplantation 4: Clofarabine combination* 5: Clofarabine monotherapy	1: Discount rates 1.5% 2: Standard parametric modeling as lower bound 3: Intention to treat 4: Exclusion future healthcare costs	1: Worst-case scenario (patients in remission have 10%-20% higher mortality rates) 2: Intention to treat	1: BRAFV600E wild mutant 2: BRAFV600E mutant 3: Stage IIIB/IIIC/IVM1a 4: Stage IVM1b/IVM1c	1: Modified societal perspective 2: 3-year effect + 3-year waning period 3: Lifetime treatment effect	1: Commercial payer perspective 2: Short-term survival (trial based)	1: Alternative utility data 2: Comparator group treated outpatient	1: A: 5-year 30%, and 20% PFS. 2: T: 5-year at 25%, and 15%. 3: Alternative payment agreement	1: Societal perspective	1: 5% reduction in long-term treatment effect >3 years 2: 10% reduction in long-term treatment effect >3 years

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Table 2. Continued

	Gong et al ²⁵	Machin et al ³¹	Lin et al ²⁴	Whittington et al (2018) ²⁶ (Kymriah)	Roth et al ²⁷	Almutairu et al ²⁸	Zimmermann et al ³⁴	Whittington et al (2019) ²⁹	Malone et al ³³	Lin & Muffly et al ³⁰	Coquerelle et al ³²	Johnson et al ³⁵
												3: 50% reduction in long-term treatment effect >3 years 4: 100% reduction in long-term treatment effect >3 years
Payment model	NR	One-off payment	Outcome-based Payment scheme	Outcome-based Payment scheme	One-off payment	NR	One-off payment	One-off payment	One-off payment	One-off payment	NR	One-off payment
Currency (year)	\$ (2013)	\$ (NR)	\$ (2017)	\$ (2017)	\$ (2017)	\$ (2017)	\$ (2017)	\$ (NR)	\$ (NR)	\$ (2018)	Euro (NR)	\$ (2018)
Discounting (effect/cost)	3%/3%	3%/3%	3%/3%	3%/3%	3%/3%	3%/3%	3%/3%	3%/3%	3%/3%	3%/3%	NR/NR	3%/3%
Outcomes												
Comparator effect (base case)	ABI: 2.70LYs/1.87 QALY Pred: 2.28LYs/1.44 QALY	6.62 QALYs	8.55 LYs 3.57 QALYs	2.43 LYs 2.10 QALYs	2.60 LYs 1.13 QALYs	0.98 PF-LYs 0.79 PF-QALYs	16.0 QALY	0.94-3.37 LYs 0.55-2.72 QALYs	7.11 LYs 5.29 QALYs	3.65LYs 1.78 QALYs	100% survival with no major complications	8.6 QALY
Intervention effect (base case)	2.44 LYs/1.60 QALYs	8.33 QALYs	20.6 LYs 8.74 QALYs	10.34 LYs 9.28 QALYs	9.49 LYs 7.67 QALYs	1.15 PF-LYs 0.95 PF-QALYs	17.3 QALY	2.83-9.19 LYs 2.07-7.62 QALYs	19.81 LYs 15.65 QALYs	A 11.8 LYs/5.50 QALYs T 8.25 LYs/3.92 QALYs	100% survival with 1 major complication	18.1 QALY
Comparator cost (base case)	ABI: \$214 584 Pred: \$44 583	\$1 693 630	\$282 000	\$337 256	\$172 737	\$132 950	\$213 399	\$108 600-151 200	\$6 316 711	\$169 000	\$215 571	\$2 780 106
Intervention cost (base case)	\$135 994	\$1 022 249	\$599 000	\$666 754	\$552 921	\$494 983	\$1 039 019	\$459 700-554 700	\$6 641 564	A \$651 000 T \$529 000	\$608 086	\$2 220 069
ICER (base case)	ABI: \$547 298 Pred: \$388 846	Dominated	\$61 000	\$45 871	\$58 146	\$2 262 706	\$643 813	\$82 400-230 900	\$31 379	A 129 000 T 168 000	NA	Dominated
BIA	NR	NR	NR	NR	NR	NR	NR	NR	NR	A \$12 billion over 5 years T \$9 billion over 5 years	NR	Treating 2000 patients expected one-time cost of \$1.7 billion
WTP threshold(s)	\$150 000	\$100 000	\$50 000, \$100 000, and \$150 000	\$50 000, \$100 000, and \$150 000	\$50 000, \$100 000, and \$150 000	\$1 683 191	\$250 000	NR	\$150 000 and \$500 000	\$50 000, \$100 000, and \$150 000	NR	\$150 000
Validation												
Sensitivity analysis	DSA, PSA, CEAC, NMB	DSA	DSA, 2-way SA, PSA	PSA	DSA, PSA, CEAC	PSA, DSA, CEAC	DSA, PSA, CEAC	NR	DSA, PSA	DSA, PSA, CEAC	Bootstrap simulation	DSA, PSA, CEAC
Checklist or validation tools	NR	NR	CHEERS checklist and Second Panel on Cost-Effectiveness in Health and Medicine recommendations	Second Panel on Cost-Effectiveness in Health and Medicine recommendations	NR	NR	NR	CHEERS checklist	NR	CHEERS checklist and Second Panel of Cost effectiveness	NR	NR

ACER indicates average cost-effectiveness ratio; CEAC, cost-effectiveness acceptability curve; CHEERS, Consolidated Health Economic Evaluation Reporting Standards; DEALE, Declining Exponential Approximation of Life Expectancy; DLBCL, diffuse large B-cell lymphoma; DSA, deterministic sensitivity analysis; HSCT, hematopoietic stem cell transplantation; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility analysis; LY, life-years; mCRPC, metastatic castration-resistant prostate cancer; NA, not applicable; NMB, net monetary benefit; NR, not reported; ORR, objective response rate; PF, progression-free; PFS, progression-free survival; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; R-DHAP, rituximab, dexamethasone, cytarabine, cisplatin; RPE, retinal pigment epithelium; SA, sensitivity analysis; SMA, spinal muscular atrophy; WTP, willingness to pay.
*Clofarabine, etoposide, cyclophosphamide

novelty of indications and technologies, but also to the combination of (high) up-front payment for uncertain long-term clinically confirmed effectiveness.

In this theme, Raymakers et al state that to quantify and characterize decision uncertainty inclusion of sensitivity analyses, especially probabilistic sensitivity analyses (PSAs), are vital and stipulated by EE best practices.¹⁴ Additionally, both Drummond et al and Jönssen et al suggest use of expected value of information

(EVI) analyses.^{6,15} Although EVI may help quantify and prioritize uncertainty, it does not directly inform reimbursement decisions and is often used to guide future investments in data collection.^{6,15} Similarly, to generate more insight in initial investment on a patient and population level, calculation of a break-even point, return of investment, and size of uncertainty are proposed by Brennan et al.⁹ Towse et al proposes use of net health effect. But whether net health effect adds anything over ICER, cost-

effectiveness acceptability curve (CEAC), and EVI remains undecided.¹⁶ A practical suggestion by Raymakers et al is to include scenarios to inform decision makers about changes in specific model parameters, for example, drug prices. In addition, Raymakers et al concludes his discussion with the request for more sophisticated modeling methodology to appropriately incorporate uncertainty and complexities of these new therapies.¹⁴ Last, Towse et al suggests more routine use of non-randomized data in EEs as well as part of the reimbursement conditions in Coverage with Evidence Development schemes to manage decision uncertainty.¹⁶

Although conducting sensitivity analyses to test impact of assumptions and model robustness on outcomes is considered good practice, not all EEs incorporated such analyses.^{44,45} Nine studies (75%) conducted a deterministic sensitivity analysis (DSA), and 9 EEs (75%) conducted a PSA. These were not necessarily the same EEs, because Machin et al conducted only a DSA³¹ and Whittington only conducted a PSA.²⁶ Six EEs (50%) report a cost-effectiveness acceptability curve,^{25,27,28,30,34,35} and 1 EE (8%) reported the net monetary benefit (NMB) measure.²⁵ Coquerelle et al reported use of a bootstrap simulation to explore uncertainty, but only reported the result of varying 2 parameters (patient weight and number of patients treated).³² Although PSAs were performed in most of the studies (75%), the interpretation and discussion of their results was found minimal. For example, none of the EEs included a PSA scatterplot in the primary article. Results of DSAs were reported in tornado diagrams. Lin and Lerman et al and Lin and Muffly et al also reported a 2-way sensitivity diagram displaying cost effectiveness at varying GT price and 5-year survival.^{24,30} EVIs were not conducted in the included EEs.

Data Extrapolation

It is common in EEs that the chosen time horizon exceeds the time frame of the (clinical) data available, especially when a lifetime horizon is applied. Data with a shorter follow-up than the evaluated time horizon require extrapolation.⁴⁶ GT trials often include single-arm studies in small patient populations with surrogate endpoints. Owing to the often deemed high unmet medical need, trials show shorter follow-up compared to more conventional products when offered to regulatory bodies.⁴⁷ Additionally, because of novel indications and treatment effects, it is uncertain if conventional extrapolation methods and distributions are appropriate for these products and if the applied surrogate endpoints are predictors for (long-term) survival.

Drummond et al proposes structural inclusion of different time horizon scenarios in evaluations to simulate different curative time frames or variance in treatment waning.⁶ Besides extrapolation of effects, Towse et al. finds assumptions should be made around the permanence of side effects.¹⁶ This comment is informed by the curative or prolonged value claim, yet he states this is not known for adverse effects. Regarding extrapolation methodology, commonly used parametric survival models (PSMs) are said to fail in properly capturing complexity of disease and underestimate survival.¹⁵ A solution mentioned is use of mixed cure models by Jönsson et al, which allows for survival to be measured for cured and non-cured patients.¹⁵ The last element mentioned is structural incorporation of treatment discontinuation, either owing to manufacturing fails or deterioration of patient health.^{14,16}

Additional survival extrapolation scenarios are observed in 6 (50%) of the studies and simulate multiple time horizons and treatment waning ranging from 0% to 100% over 3 to 5 years.^{24,26,27,30,34,35} The outcome of these scenarios shows large

variance. Nevertheless, which scenario best represents clinical practice is found difficult to assess and can only be informed by continued clinical follow-up or expert opinion. Gong et al, dating from 2013 and the oldest study included, used the Declining Exponential Approximation of Life Expectancy method to extrapolate data.^{25,48} The Declining Exponential Approximation of Life Expectancy method was popular in the 1980s to 1990s but lost traction owing to introduction of more sophisticated methods. Nowadays other methods such as PSMs or hazard models are more common. PSMs were applied in 7 EEs (58%).^{26-29,33-35} Almutairi et al and Zimmerman et al both applied 1 PSM model, respectively, the Weibull and exponential.^{28,34} The reasoning behind their choices lacks. The other 5 EEs using PSMs explore between 4 and 7 different monotonic and non-monotonic hazard models for best fit^{26,27,29,33,35} via visual inspection, Akaike Information Criterion and Bayesian Information Criterion metrics, or expert opinion. Whittington et al modeled 6 PSMs. Instead of determining best fit, the authors used the extreme outcomes as a range for both effect and cost outcomes.²⁹ This results in an ICER estimate between \$82 400 and \$230 900. Less common extrapolation methods applied are piecewise exponential function and model calibration.^{24,30} Coquerelle et al did not extrapolate data, because the chosen 2-year time horizon for the analysis was directly informed by 2 years of clinical data.³² Machin et al did not report how data were extrapolated.³¹

Discount Rates

In EEs, the timing of incurred cost and effects is relevant, because people generally value future costs and effects less with value diminishing over time.⁴⁹ Therefore, the value of costs and effects are adjusted with an annual rate for the time at which they occur. This adjustment is known as discounting.⁴⁹ In the case of GTs, payment is often requested up front while the benefits are claimed to last for multiple years. Therefore, the discrepancy between time of cost and effect is much larger than in more conventional and chronic treatments.

Discount rates are specifically addressed by 3 commentaries.^{6,15,16} Methodological adjustments are proposed by Jönsson et al, who advocate to apply 1.5% to 3.0% lower discount rates for effect than cost.¹⁵ Drummond et al agrees to apply lower discount rates for effect compared to cost, because this would value the current relative size of the irreversible effect at present time higher, but they do not provide a quantification.⁶ Jönsson et al proposes application of differential discounting. To evaluate the impact, Drummond and Towse et al propose to include discount rates as a parameter in deterministic sensitivity analyses (DSA) varying between 0% and 5%.¹⁰

Variation in discount rate is applied by Whittington et al in a separate scenario and showed to have a considerable impact on the ICER value.²⁶ Base case (3% discount rate) yielded an ICER of \$46 000 per QALY and scenario analysis (1.5% discount rate effect) estimated an ICER of \$37 000 per QALY. With the exception of Whittington et al,²⁶ no specific attention is given to discount rates in the included EEs. All evaluations that addressed discounting applied a rate of 3% to effects and costs, which is based on recommendations of the first panel on cost-effectiveness.⁵⁰ In the 9 DSAs reported by the 12 EEs (75%), discount rates appear in 4 analyses in the top 10 (ranked between 2 and 9) most sensitive parameters.^{24,25,27,30} In the study by Roth et al, the only study in which the DSA figure included exact numbers of parameter variation impact, varying the discount rate between 1% and 5% resulted in an ICER estimate between \$3980 and \$74 918.²⁷ Whether the discount rates were not included in the remaining 5 studies or were not found to be sensitive enough to be reported in the DSA is unclear.

Novel Value Elements

The considerations included in this theme include discussions of whether benefit of GTs may include more than increased length and quality of life.⁶ Similar to the discussions around (re)definition of applied perspectives, new treatment opportunities may introduce novel value elements and benefits across domains. Examples of such benefits according to Drummond et al and Jönssen et al are the value forgone in other disease areas, valuation of cure as opposed to wider incremental benefits, social value beyond health gain, patient preferences for treatments beyond health gain, process utilities, option value, and value of spillovers linked to innovation.^{6,15} Some of these proposed elements are difficult to quantify, such as scientific spillover, option value, or value foregone for other disease areas. Yet others can be quantified with existing methods, such as reiterated by Barlow et al, who advocate structural use of multicriteria decision modeling.⁸ Incorporation of disease severity, as mentioned by Garrison et al,¹¹ is more of a policy consideration also heard outside of the GT space.^{51,52} Consequently, keeping in mind most GTs in development claim to address high unmet medical need populations, the last consideration can potentially have considerable impact.

Most reported outcomes in included EEs are life-years (LYs), quality-adjusted life-years (QALYs), cost, and ICER. Gong et al additionally reports an average cost-effectiveness ratio²⁵ and Almutairi progression-free (PF) LYs, PF QALYs, PF ICER, and PF incremental cost-utility ratio, as well as a disease-specific measure, objective response rate.²⁸ The study by Zimmerman also reports disease specific measures visual acuity and visual function.³⁴ None of the novel value elements discussed in the perspective article are incorporated in the published EEs.

Use of Indirect Comparisons and Surrogate Endpoints

Evidence generation in new and orphan indications is associated with challenges around small sample sizes, little historical data, disease knowledge, and limited associations between surrogate and hard endpoints.⁵³ The evidence base currently supporting decisions around GTs consists of mostly short-term studies with surrogate (novel) endpoints.⁵³

Drummond et al justifies use of such data partially by transparency around validation attempts to properly combine data sources.⁶ Barlow et al and Drummond et al justify use of historical data under certain conditions; homogeneous population, when confounding factors are well known, when patient management is established and standardized, when the primary endpoint is objective and robust, and when the effect size of the new therapy is substantial versus the historical cohort.⁶

The included EEs have seemingly given little attention to the validity and generalizability of applied endpoints. Although few surrogate endpoints are included in the EEs, most outcomes are expressed as an ICER. Only 3 studies (25%) had the availability of direct clinical comparison.^{28,32,35} The remaining 9 EEs (75%) dedicated little words to any comparability or adjustment analyses performed when combining clinical data sources.

Discussion

With several new GTs expected to apply for market authorization in the next few years, the high prices combined with uncertain value claims of these products cause concern.² This is reflected in recent commentaries addressing valuation, affordability, and payment of GTs. Here, we created an overview of methodological considerations described in these commentaries and assessed their application in published peer-reviewed EEs.

The identified considerations were grouped in 7 themes: payment models, (re)definition or perspectives, addressing uncertainty, data extrapolations, discount rates, novel value elements, and use of indirect comparisons and surrogate endpoints. We searched for EEs of GTs in the literature and assessed their quality of reporting using CHEERS. Additionally, we explored whether the identified methodological elements were applied in these evaluations. We found that the reporting quality of these EEs in general was acceptable to good. The proposed methodological elements were incorporated in a minority of these published EEs. Yet, the few EEs that did include these considerations in their evaluation showed substantial impact. To our knowledge, this is the first review that has taken this approach.

Taking a closer look at the identified methodological considerations and placing them into a broader context, it stands out that VBP is only mentioned twice as a suitable alternative payment model. VBP has taken a flight in the recent years and is often mentioned in discussions around affordability of personalized medicines.⁵⁴ Perhaps this observation is linked to the identified theme: novel value elements and (re)definition of perspectives. Unclear definition and calculation of (added) value of these curative therapies makes pricing based on their value difficult. In the 2 studies that did include an alternative payment model with performance assessment, the assessment of treatment response occurred within 1 to 3 months after admission.^{24,26} One can argue whether assessment after such short time is appropriate for a product with a multiyear curative claim, and whether maximum treatment potential is reached at point of assessment. In literature when referring to annuity-based or pay-for-performance payment models, a multiyear payment plan is meant.^{6,11,15,16,37}

Regarding perspectives, we noticed the included cost and benefits do not always comply with the definitions in guidelines and literature.^{32,35,45} This phenomenon is previously described in the literature.⁵⁵ When exploring novel value elements and considering (re)definition of perspectives for novel therapies, it is important to be transparent in applied methodologies and adhere to claimed definitions. Another difficulty when discussing perspectives is country preference. For example, in the United States mostly the healthcare payer perspective is applied. In the United Kingdom, NICE asks for a National Healthcare Service perspective, and French guidelines specifically ask for an all-payers perspective.^{42,56} More elements, in which country-specific preferences play a role, are utility measures and discount rates. To illustrate, the Dutch National Healthcare Institute requests application of differential discounting with higher effect (1.5%) than cost (4.5%) percentages in their evaluations,⁵⁷ and UK NICE requests 3.5% for both cost and effects.⁴² The commentaries seem to agree that current discount rate preferences are worth revisiting, but no uniform recommendation could be formulated. Admittedly, the US Second Panel on Cost-Effectiveness in Health and Medicine adheres to the recommendation given by the first panel, but the authors also mention the commonly applied 3% might be too high, especially from a healthcare perspective.⁴⁹ Therefore, when changes are proposed to specific elements such as perspectives, novel value elements, or discount rates, it is not only important to align with the decision makers, but also to realize specific methodological considerations can differ per country.

Deterministic and PSAs are often requested in HTA authority guidelines, and their application and interpretation are considered good practice health economics.^{42,57,58} Nevertheless, we find only 75% of EEs included a DSA or a PSA. Moreover, in the EEs in which modelers did conduct a sensitivity analysis, the interpretation and discussion of results and impact was found minimal. This is especially surprising, because discussions around GT EEs are dominated by perceived uncertainties.^{6,14-16,37} More advanced

analyses to explore and quantify uncertainty were proposed in the perspectives such as EVI.^{6,15} Currently no EVI analyses for GTs were found in the literature. Given limited resources and high-burden disease, conducting such an analysis can help guide investment and prioritization setting in additional research, although this is perhaps more of interest to developers and investors than EEs for HTA. Further, a need is expressed by Raymakers et al to use and develop methods that can contribute to reducing uncertainty in EEs.¹⁴ More sophisticated methods can be insightful in the identification and quantification uncertainty. Additionally, it is proposed elsewhere that authorities should also learn how to become more comfortable making decisions under uncertainty.⁴³ The latter could help increase organizational readiness of HTA organizations to cope with the emerging GT pipeline as well as prepare for inevitable introduction of innovative products in the future.⁵⁹

When assessing the methodological elements, a distinction can be made between considerations specific for GTs and more generic considerations. One of the characteristics that makes the EE of GTs different in the current policy environment is their curative claim in combination with high up-front payment and uncertain longitudinal effectiveness data. This is reflected in the most often-mentioned element: payment models. These alternative payment models aim to share risk between developer and payer and spread payment over time. Another predominantly GT-specific element is discounting rates. This theme was also discussed in NICE's mock appraisal and the Valuing a Cure technical brief by the Institute for Clinical and Economic Review.^{7,20} Similar arguments as we found are put forth in these reports, stating effects should be discounted at a lower rate than costs reflecting higher present value for future effects. Next, the promise of cure for novel and previously debilitating disease may influence the definition of perspectives and novel value elements. Both considerations address the underlying assumption that GTs may be accompanied by benefits other than prolonged life and increased quality of life. The redefinition of perspectives theme presents this by stating that benefits are achieved in the personal, social, and economic domains with a greater impact for society.³⁷ Novel value elements have previously been discussed in a broader context outside of the GT field, as well as the use of multi-criteria decision analyses to support the complex decision making.⁶⁰ Other elements mentioned—addressing uncertainty, data extrapolation, and use of indirect comparisons and surrogate endpoints—can also be attributed to the intended indications, which currently are mostly orphan disease and new indications. Orphan indications are associated with little and single-arm data, making use of indirect comparisons or historical comparisons necessary.⁶¹ The GT field can therefore acquire information from learning elsewhere and vice versa.

Study Limitations

Despite our best efforts, this study had some limitations. One limitation of our study was that only perspectives and EEs published in peer-reviewed literature were included. As a result, methodological considerations and evaluations reported elsewhere (eg, conferences, white papers, HTA dossiers) were excluded from this research. The second limitation was that 11 of 12 identified EEs were conducted from a US perspective, which may limit generalizability. Nevertheless, when comparing our results to recent non-peer-reviewed reports such as the NICE mock appraisal in the United Kingdom and a value assessment conducted by the US-based Institute for Clinical and Economic

Review, we find similar findings and recommendations.^{7,20} Compared to the EEs, the authors of the included commentaries have a more global spread, giving the methodological considerations a more global character. A third limitation could be that most commentaries were published before or around the same time as the included EEs. This allows for little spillover of the discussed considerations in the identified EEs. Nevertheless, it is not our intent to score the included EEs to which extent they include the proposed methodological elements. We intended to create a timely overview of current practices around EEs specific for GTs and explore their impact and implementation. Similarly, we observe that all but 1 of the included EEs were published in 2018 and 2019. This emphasizes the relevance and timeliness of this topic. Therefore, periodic reassessment of this analysis could be of interest to track both the methodological discussions as well as the implementation and impact. To continue, we only included articles published between 2007 and August 2019, which may have omitted earlier or future GT EEs. We chose 2007 as a starting point because this is the year in which GTs were first formally defined as medicinal products.¹⁹ Last, we used the CHEERS checklist to assess the quality of reporting of included EEs.²² We did not systematically assess the risk of bias within or across studies. Although several tools are developed to assess different types of bias, we found systematic assessment was out of scope for this research.⁶² Additional to the quality-of-reporting assessment using CHEERS, we aimed to critically reflect on sources, methods, and assumptions applied in included studies.

Implications and Recommendations for Future Practices and Research

Given the unique and novel characteristics of curative GTs, a lively discussion is seen in the literature addressing affordability and methods for proper value estimation.^{63,64} Following the commentaries included in this review, more are to be expected.^{63,64} So far, this is the first research to systematically summarize current considerations and explored their applications. Yet, no work is done to assess the appropriateness of these novel considerations. The fundamental question underlying this work is whether EEs of curative GTs are essentially different from other interventions. Our research suggests at least the EEs of GTs are not radically different from evaluations of more conventional medicinal products, but only few elements may need adjustment. We therefore recommend future research to explore, per element, which approach is best suitable and appropriate for economic models of curative GTs. This review aims to provide an overview and prioritization of methodological elements to investigate. Furthermore, when combining these elements, this may lead to development of a curative GT-specific model. Similarly to disease-specific models, a standard curative GT model can improve comparability of future health EEs and increase uniformity in modeling choices.⁶⁵ According to this study, this model should at least address discounting rate, different perspectives and scenarios that explore the impact of payment models, and treatment waning. When input parameters are highly uncertain, scenario analyses should be included to explore the impact of different assumptions. In addition to the methodological uniformity, we strongly recommend both DSA and PSA to be routinely included and reported.

To conclude, we created a timely overview of methodological considerations discussed in the literature specifically addressing EEs of GTs. We found that these elements, to date, are hardly applied and explored in peer-reviewed published evaluations. The

few EEs that do explore these elements show they have considerable impact. This shows that although an EE may be considered of sufficient reporting quality according to accepted CHEERS standards, it may lack informativeness.⁶⁶ Future research should explore, per element, if and how the element is appropriate for routine application in economic models of GTs. Development and implementation of methodological recommendations for EEs should occur in collaboration with payers and authorities whose decisions these evaluations aim to inform.

Supplemental Material

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.jval.2020.04.1833>.

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