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HTA Challenges for Cell and Gene (C&G) Therapies

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Disclaimer

- Speaking and consultancy fees: Amgen, Daicchi Sankyo, Janssen, Novartis, Pfizer, Takeda.

Background

- Unique opportunities for improving patient management but also important challenges
- First indications in small populations but significant pipeline activity
  - *30-60 products by 2030; $12.5-$100bn haematological cancer treatment costs**
- Separate HTA process for C&G therapies not yet developed
  - *High levels of clinical uncertainty*
  - *Affordability and budget impact concerns*
- Risk sharing and 'managed entry' agreements (MEA) key to initial approvals
- Concerns remain over affordability and different market dynamics

* Quinn C et al. Estimating the clinical pipeline of cell and gene therapies and their potential economic impact on the US healthcare system. Value Health. 2019;22(6):621–626.

What is HTA?

Health Technology Assessment (HTA)

- Assesses the added value of a new health technology compared to the current standard of care
- Therapeutic effect, side-effects, impact on quality of life and costs
- Systematic and multidisciplinary process

Purpose

- Provide policy-makers with evidence based information, so they can formulate health policies that are safe, effective, patient-focused and cost-effective

International examples

- England (NICE), France (HAS), Germany (G-BA)
- Australia (PBAC), Canada (CADTH), Thailand (HITAP)

Key HTA challenges for C&G therapies

Evidential

- Surrogate endpoints
- Curative potential
- Small trials
- Historical data comparisons
- Generalizability of evidence from specialist centers

Price and affordability

- One-time administration
- Large upfront price
- Infrastructure costs
- "Real challenge is not HTA but budget impact" (Towse, 2014)

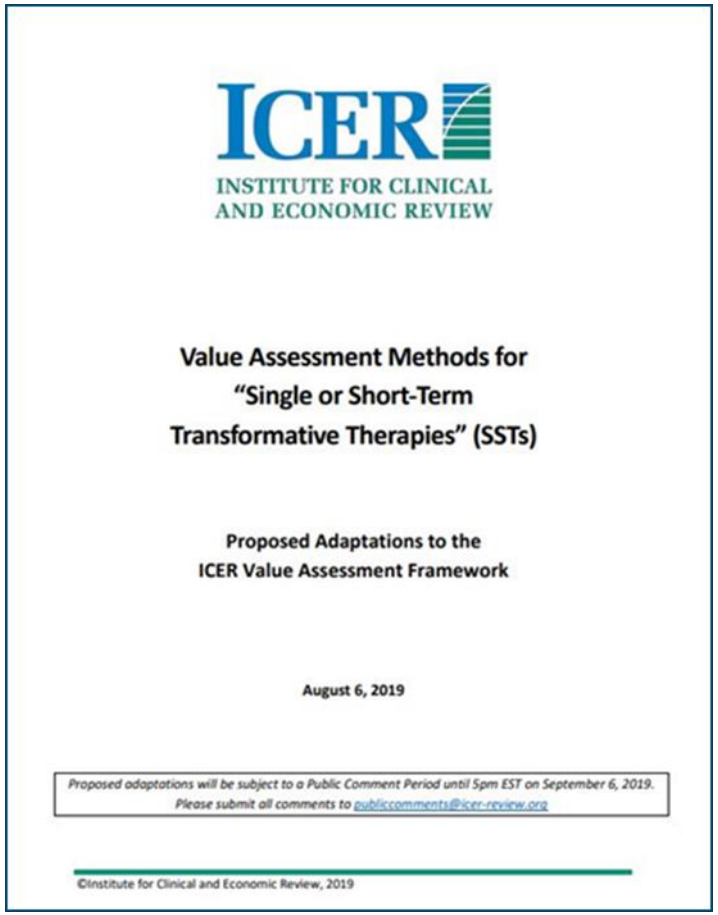
Uncertainty

- Uncertain duration of benefit
- Strength of surrogate relationships
- Type of managed entry agreement

I. Outcome based

II. Financial based

Are existing HTA processes fit for purpose for CAR-T?



ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Value Assessment Methods for "Single or Short-Term Transformative Therapies" (SSTs)

Proposed Adaptations to the ICER Value Assessment Framework

August 6, 2019

Proposed adaptations will be subject to a Public Comment Period until 5pm EST on September 6, 2019. Please submit all comments to publiccomments@icer-review.org

Exploring the assessment and appraisal of regenerative medicines and cell therapy products

Produced by Centre for Health Technology Evaluation, National Institute for Health and Care Excellence (NICE)

Authors Nick Crabb, Programme Director, Scientific Affairs
Andrew Stevens, Technology Appraisals Committee Chair

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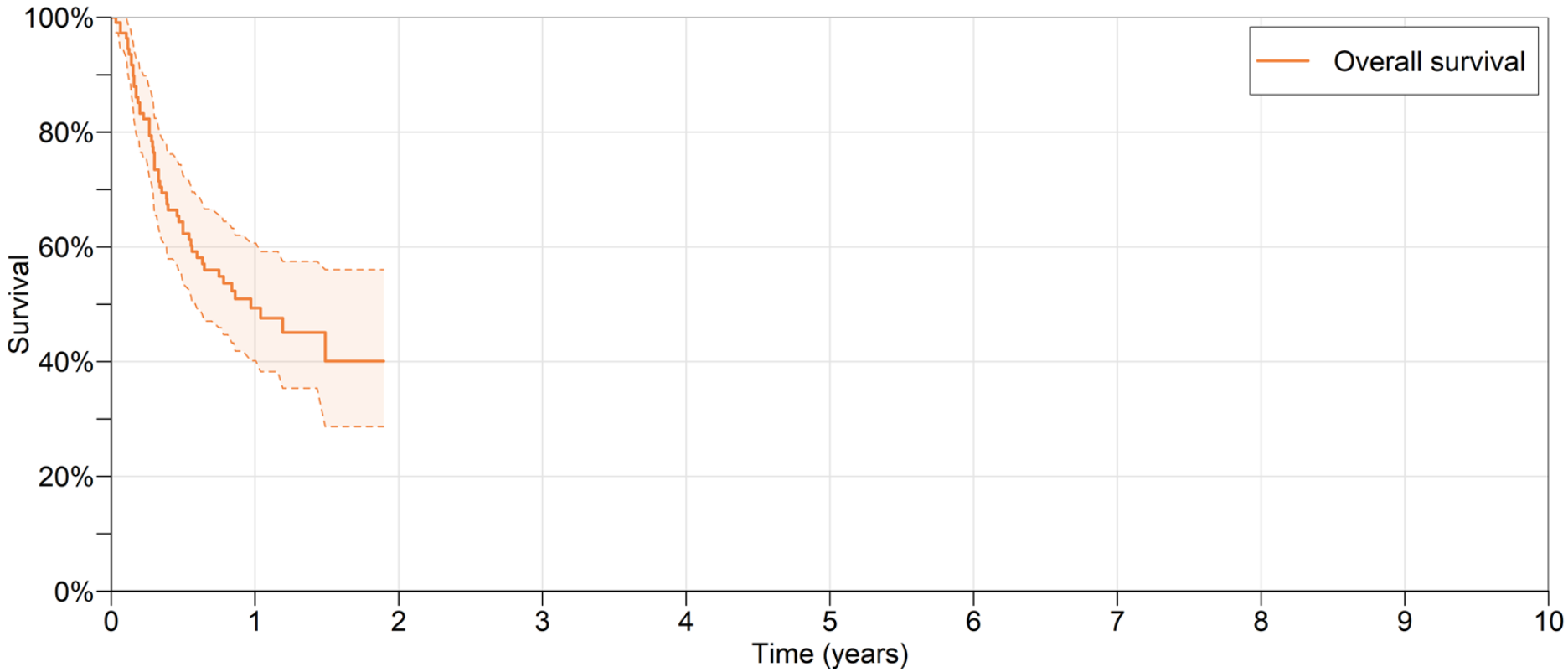
Conclusions from UK (NICE) and USA (ICER)

- **NICE**
  - Existing methodology and decision framework is applicable
  - Decision uncertainty a major factor
  - Practical, workable payment methodologies important in managing uncertainties and facilitating early patient access
- **ICER**
  - Core elements of ICER's assessments are suitable
  - Adaptations may help address distinctive issues:
    - Relationship of evidence to value
    - Transparent and consistency in approach to elements of additional value (QALY weights/modifiers)
    - Broader societal discussion on how to share economic surplus (different market dynamics)

General learnings from UK HTA appraisals of CAR-T

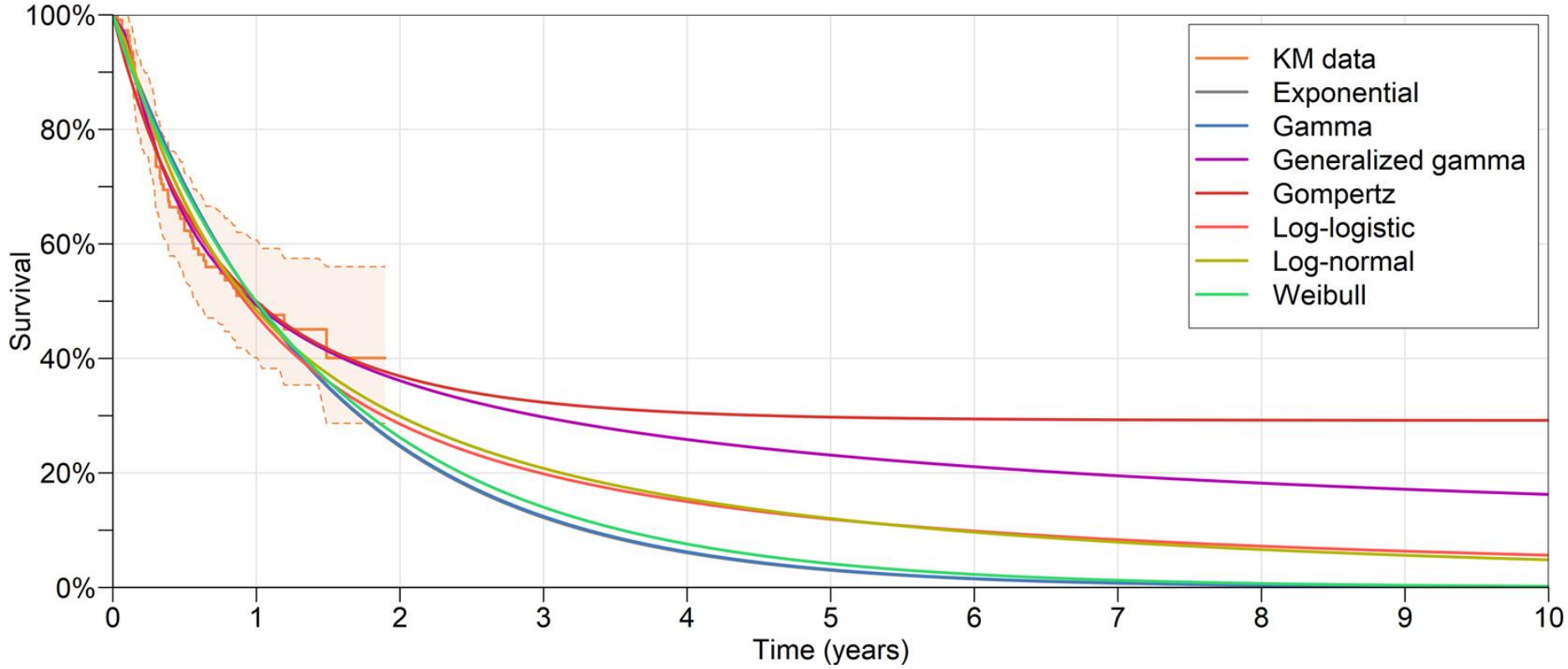
Target population and proposed positioning critical	• Marketing authorization broader than trial populations • Concerns over relevant comparator/standard of care
Violation of ITT principle	• Manufacturing failures • Death prior to infusion
Extrapolation approaches central	• Cure? Longer term excess mortality? Possible late relapse? • Implications for HRQoL and cost assumptions
Resource and cost uncertainties	• Bridging vs lymphodepleting chemotherapy • Administration and monitoring requirements (inpatient vs ambulatory) • Management of AEs (CRS and B-cell aplasia; ICU; readmission)
Implementation issues	• New service specification and phased implementation • Training requirements

Extrapolating survival

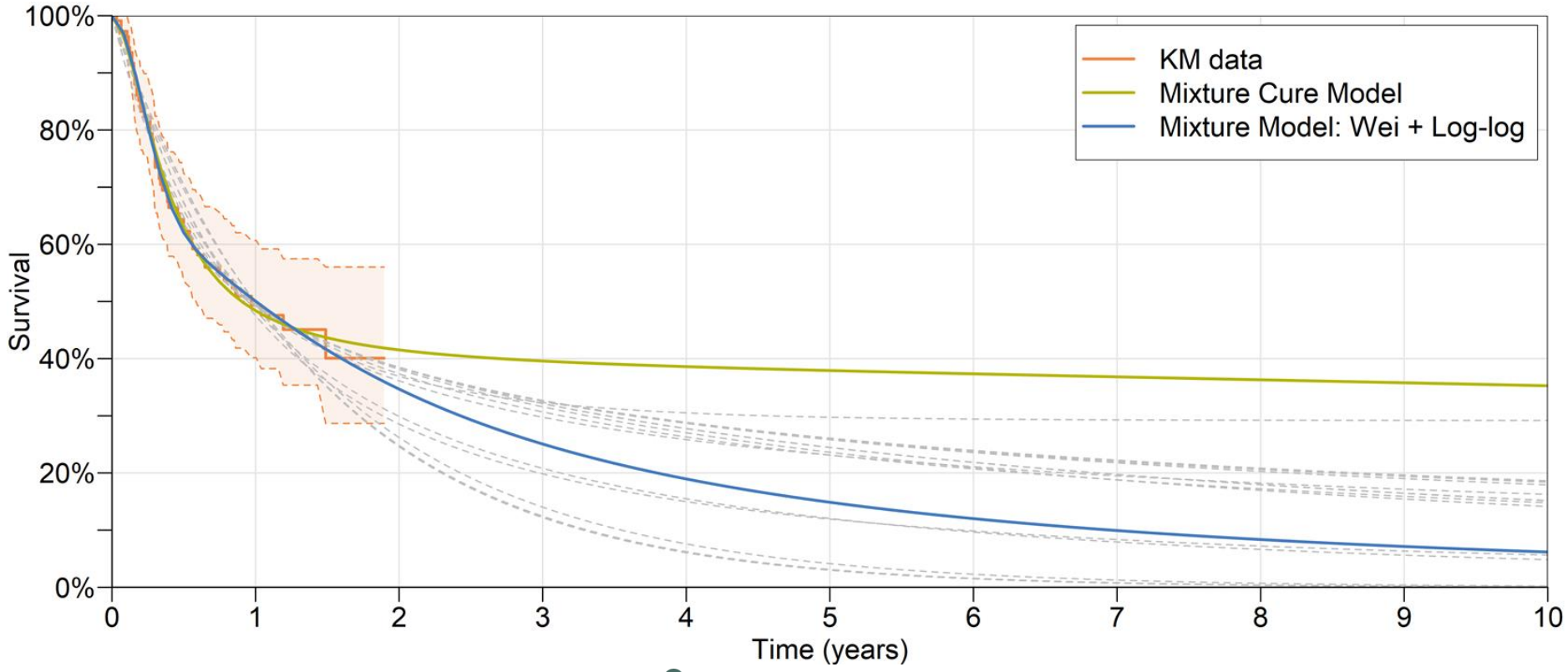


Data source: Tisagenlecleucel (Kymriah®) overall survival, as reported by Schuster et al. (2018). DOI: 10.1056/NEJMoa1804980
Data replication method: Guyot et al. (2012). DOI: 10.1186/1471-2288-12-9

Extrapolating survival

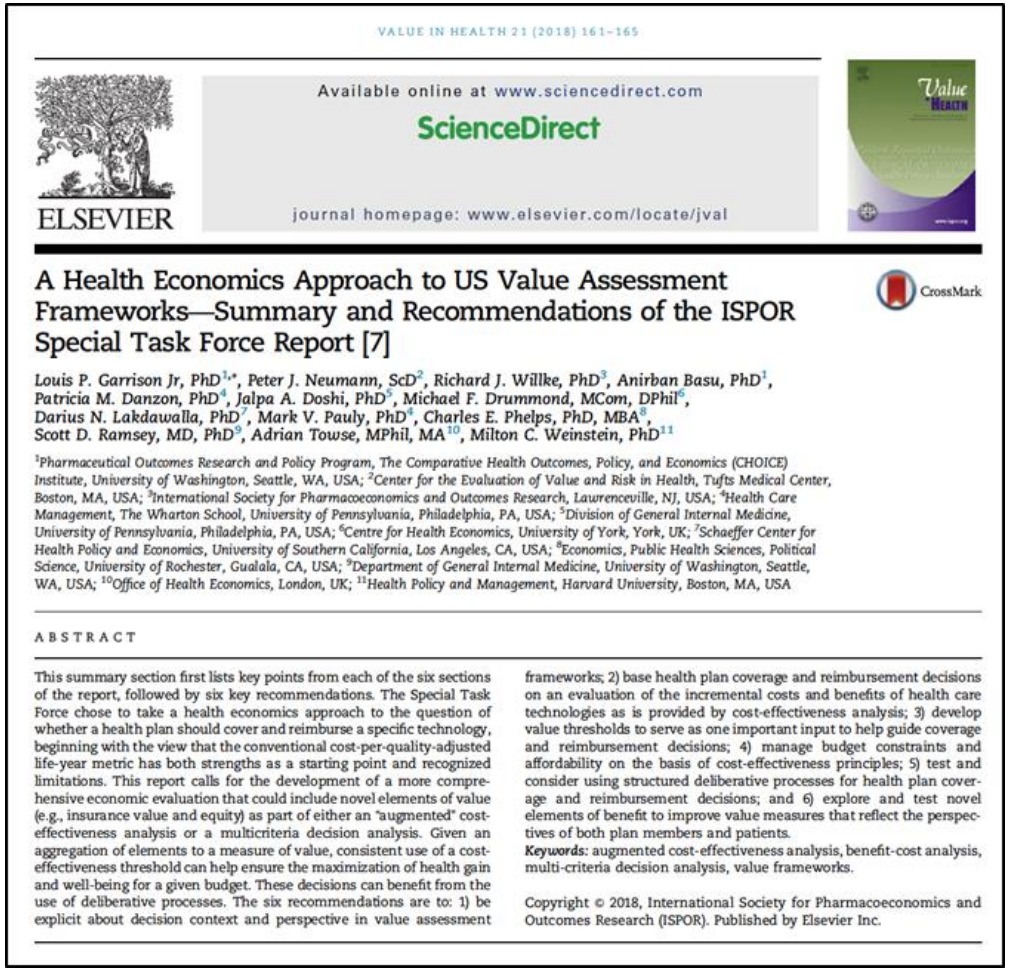


Extrapolating survival



NICE Reference Case (UK)

- Use of the Quality-Adjusted Life Year (QALY) central
- Health service perspective for costs
- Range of motivating factors
  - The nature of NICE's decisions
  - Consistency between appraisals
  - Consistency within appraisals
- Reference case ≠ standardisation



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A Health Economics Approach to US Value Assessment Frameworks—Summary and Recommendations of the ISPOR Special Task Force Report [7]

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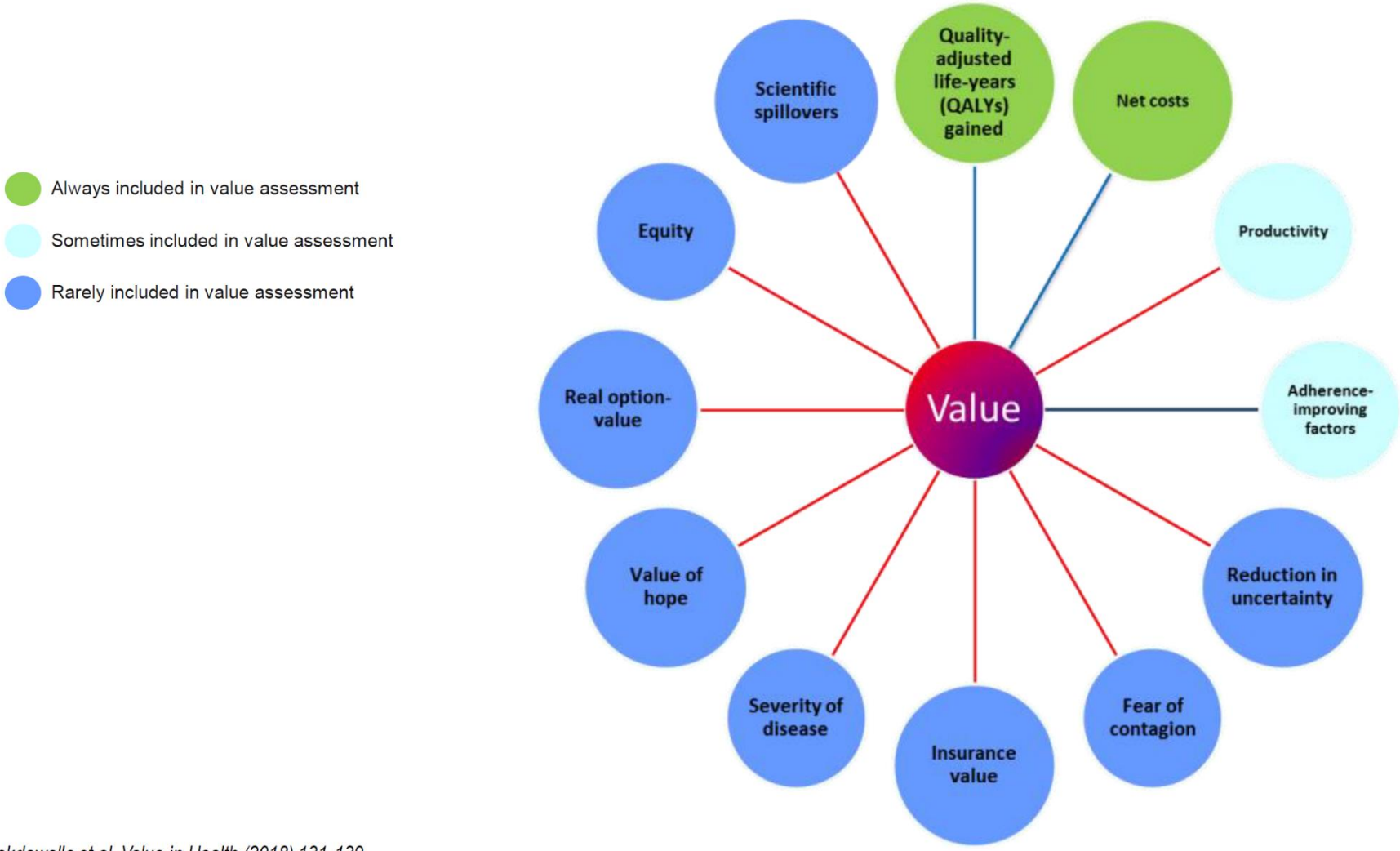
ABSTRACT

This summary section first lists key points from each of the six sections of the report, followed by six key recommendations. The Special Task Force chose to take a health economics approach to the question of whether a health plan should cover and reimburse a specific technology, beginning with the view that the conventional cost-per-quality-adjusted life-year metric has both strengths as a starting point and recognized limitations. This report calls for the development of a more comprehensive economic evaluation that could include novel elements of value (e.g., insurance value and equity) as part of either an "augmented" cost-effectiveness analysis or a multicriteria decision analysis. Given an aggregation of elements to a measure of value, consistent use of a cost-effectiveness threshold can help ensure the maximization of health gain and well-being for a given budget. These decisions can benefit from the use of deliberative processes. The six recommendations are to: 1) be explicit about decision context and perspective in value assessment frameworks; 2) base health plan coverage and reimbursement decisions on an evaluation of the incremental costs and benefits of health care technologies as is provided by cost-effectiveness analysis; 3) develop value thresholds to serve as one important input to help guide coverage and reimbursement decisions; 4) manage budget constraints and affordability on the basis of cost-effectiveness principles; 5) test and consider using structured deliberative processes for health plan coverage and reimbursement decisions; and 6) explore and test novel elements of benefit to improve value measures that reflect the perspectives of both plan members and patients.

Keywords: augmented cost-effectiveness analysis, benefit-cost analysis, multi-criteria decision analysis, value frameworks.

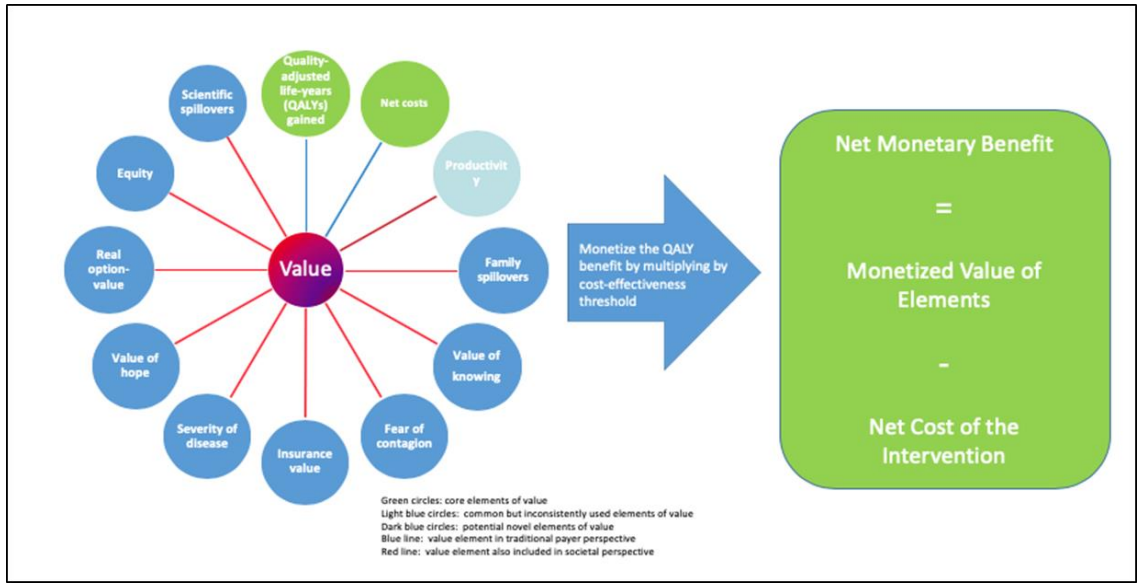
- 1. **Cost-per-QALY analyses have strengths and limitations**
- 2. Frameworks that **focus on coverage/reimbursement** should **consider cost per QALY, as a starting point**
- 3. **Consider elements not normally included in CEAs** (e.g., severity of illness, equity, risk protection) but **more research needed.**
- 4. Test and consider using structured deliberative processes

Additional elements of value for C&G therapies?

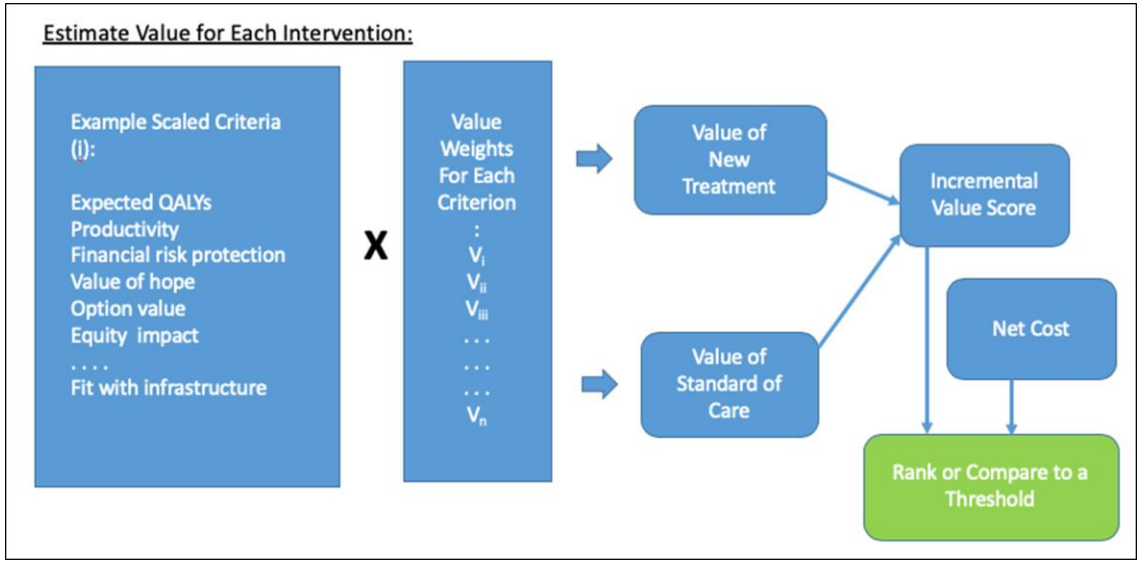


Source: Lakdawalla et al. Value in Health (2018) 131-139

Augmented cost-effectiveness analysis



Multi-criteria decision analysis



Structured deliberative processes

- No existing method of aggregation is perfect
  - Pragmatic approaches needed
  - Severity weights already reality
  - Equity adjusted approaches developing
- Advantages of structured deliberation
  - Transparency and accountability
  - Consistency
- Cost per QALY widely used starting point (US and Europe)
  - 'Aid to' rather than 'substitute for' informed decision making

Proposed checklist for C&G therapies

Item	Yes	No	Notes
Clinical effectiveness			
Surrogate endpoint used	☐	☐	Validation given?
Rare disease	☐	☐	Prevalence _____
Serious condition	☐	☐	
Single-arm trial	☐	☐	Matched historical cohort used?
Pediatric population	☐	☐	Age range _____
Reporting of adverse consequences and risks	☐	☐	
Size of clinical trial	____ number of patients		
Length of clinical trial	____ duration in months		
Extrapolation to long-term outcomes	____ duration in months		
	Yes	No	Quantification
Elements of value			
Severe disease	☐	☐	
Value to caregivers	☐	☐	
Insurance value	☐	☐	
Scientific spillovers	☐	☐	
Lack of alternatives	☐	☐	
Substantial improvement in life expectancy	☐	☐	
	Yes	No	Notes
Other considerations			
Discounting			
Different discount rates explored	☐	☐	
Uncertainty			
Alternative payment models explored	☐	☐	

CDDF Cancer Drug Development Forum

Drummond et al. Value in Health. 2019; 22(6): 661–668

Managing uncertainty and risk sharing

- One-off treatment cost increases financial risk
  - Irrecoverable costs vs repeat treatment
- Financial arrangements/risk sharing can eliminate additional risks
  - Outcomes-related payment and amortization particularly relevant
- Schemes should entail genuine and appropriate sharing of risk at the point of approval
- Need greater awareness and consistency in the application of methods to address financial risks

Budget impact and affordability

- Broader challenges to conventional HTA methods
  - Affordability and 'fair-price' concerns
  - Prevalent population and first-mover advantage
  - Limited potential for brand-to-brand competition; Lack of generic entry
- Development of HTA approaches which explicitly consider sharing of surplus distribution
  - QALY cap (no allowance for cost-offsets)
  - Mock patent cliff (allowance for cost-offsets for specific period)
  - Shared savings (% of cost offsets)

Conclusions

- CAR-T is a ground-breaking therapy
  - Conventional value/HTA frameworks have been successfully applied to CAR-T but many challenges from study designs
  - Further research needed on distinctive features not captured in QALY
  - Important role for structured deliberative process

- Managed entry and flexible pricing important for initial approvals
  - Need for constructive dialogue between stakeholders - progressive reflection of value as knowledge increases
  - Scope to better communicate benefits of access vs risks/uncertainties under different scenarios