Health Technology Assessment for Gene Therapies: Are Our Methods Fit for Purpose?— A Health Economist's Perspective

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- These are my views and not necessarily those of any co-authors.

What is the issue?

Gene-targeted therapies are in development for a range of severe and rare health conditions.

- They involve an ”one-time”, upfront treatment with the health gains (in terms of length of life and quality of life) over many years.
- That health gain can be very large—hence, the “value” is very large.
- Uncertainties make it difficult to calculate that value at launch.

Two questions:

1. How do we finance these payments?
2. **Are we providing an appropriate reward or incentive for the innovation? How should that reward be determined?**

ISPOR Special Task Force (2018)

Recommendation II (of VI): Base health plan coverage and reimbursement decisions on an evaluation of the incremental costs and benefits of healthcare technologies as is provided by cost-effectiveness analysis.

1. **Cost-per-QALY analyses have strengths and limitations**

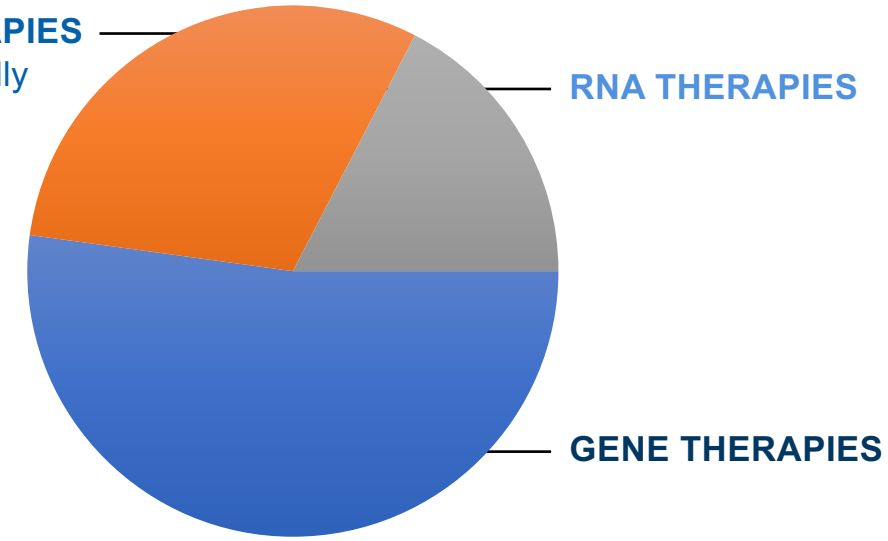
2. Frameworks that **focus on coverage/reimbursement** should **consider cost per QALY, as a starting point**

3. **Consider elements not normally included in CEAs (e.g.,** severity of illness, equity, risk protection) but **more research needed**.

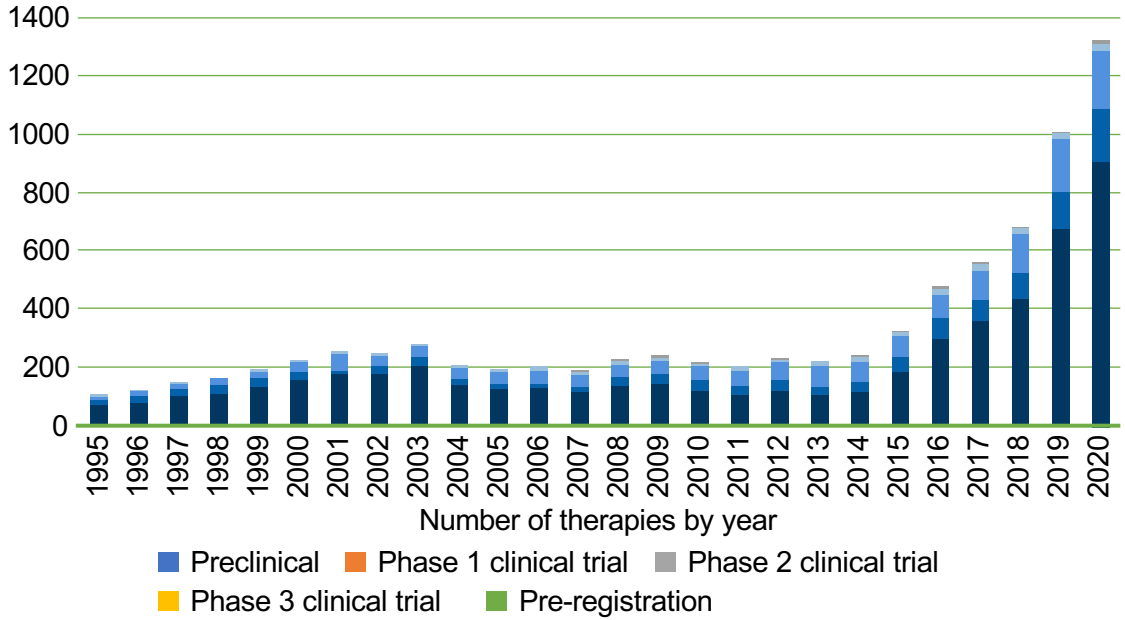
Source: STF Final Report, ViH, Feb. 2018

Rapid Growth in the Gene Therapy Pipeline

Pipeline Therapies by Category



Gene Therapy Pipeline



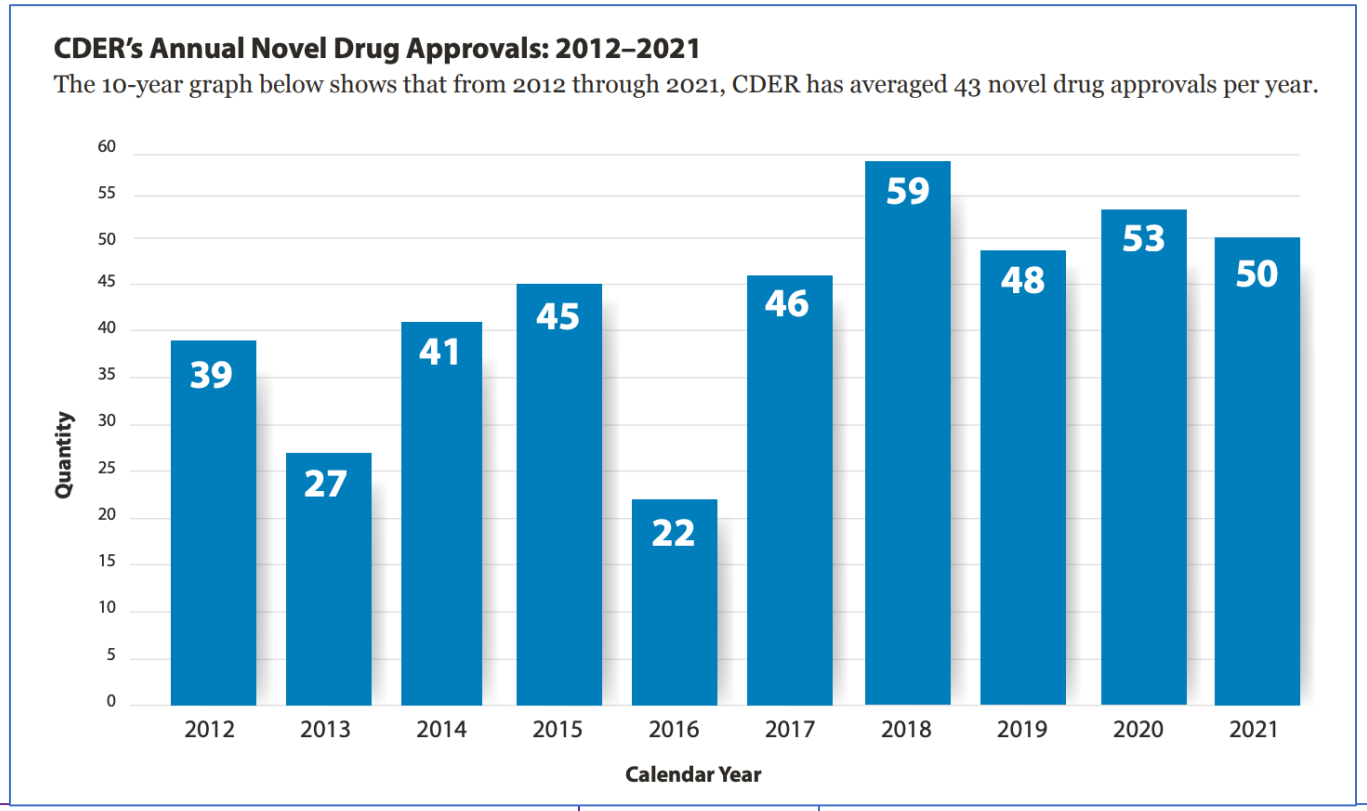
The number of gene therapy clinical trials has significantly increased over the last 30 years, with an increasing number of investigational new drug (IND) applications[2,3]

IND, investigational new drug.

Figure. with permission from American Society of Gene and Cell Therapy.[1]

1. American Society of Gene and Cell Therapy (April 2021). Accessed May 11, 2021. https://asgct.org/global/documents/asgct-pharma-intelligence-quarterly-report-q1-2021.aspx **2.** Ginn SL et al. *J Gene Med.* 2018;20:e3015. **3.** Eisenman D. *Applied Biosafety: J ABSA International.* 2019;24(3):147-152

CDER's Annual Novel Drug Approvals, 2012-2021



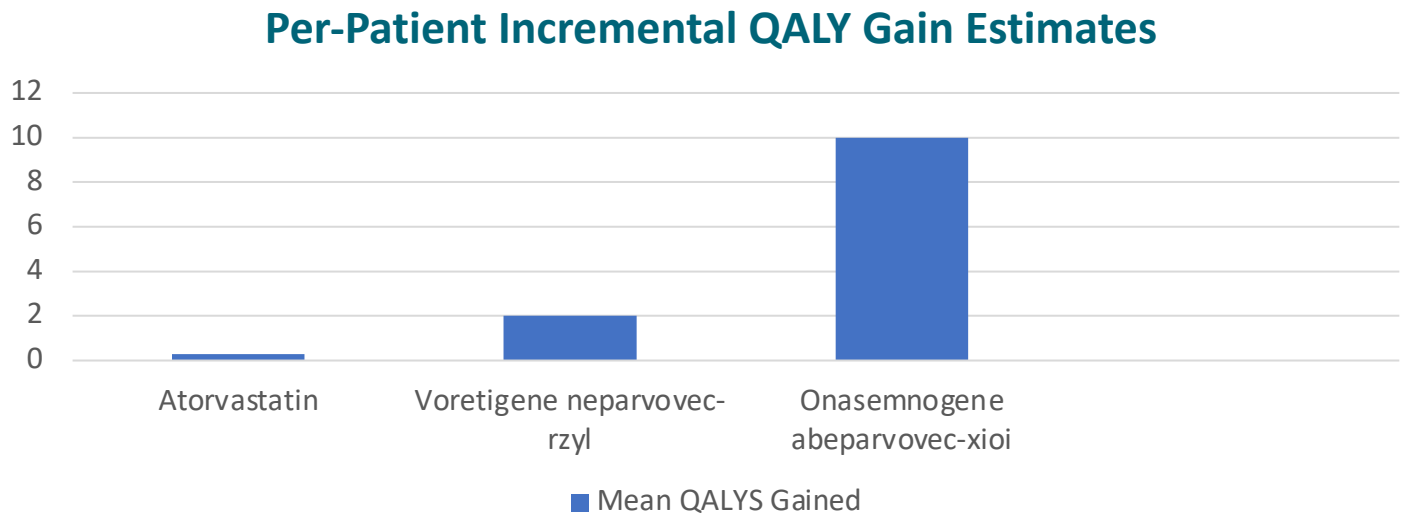
In 2021:

- 54%— as first-in-class
- **52%—for rare or orphan diseases**
- **28%—accelerated approval**
- 28%—as breakthrough therapies
- 68%—designated Priority Review

New drugs:

- **High risk/high reward**
- **Global public goods**
- **Few annually**
- **Productivity flat over time**
- **Mix constantly changing**

Lifetime Incremental Quality-Adjusted Life-Years Gained of Gene-Targeted versus Chronic Treatment



Gene-targeted therapies can provide large improvements in expected QALYs gained.

Sources:
Lin L et al. Cardiovascular Drugs Ther 2015; 29: 187-197 Zimmermann M et al. *Value Health Reg Issues*. 2019;22(2):161-167.;. ICER (2019). Accessed May 27, 2021. https://icer.org/wp-content/uploads/2020/10/Valuing-a-Cure-Technical-Brief.pdf

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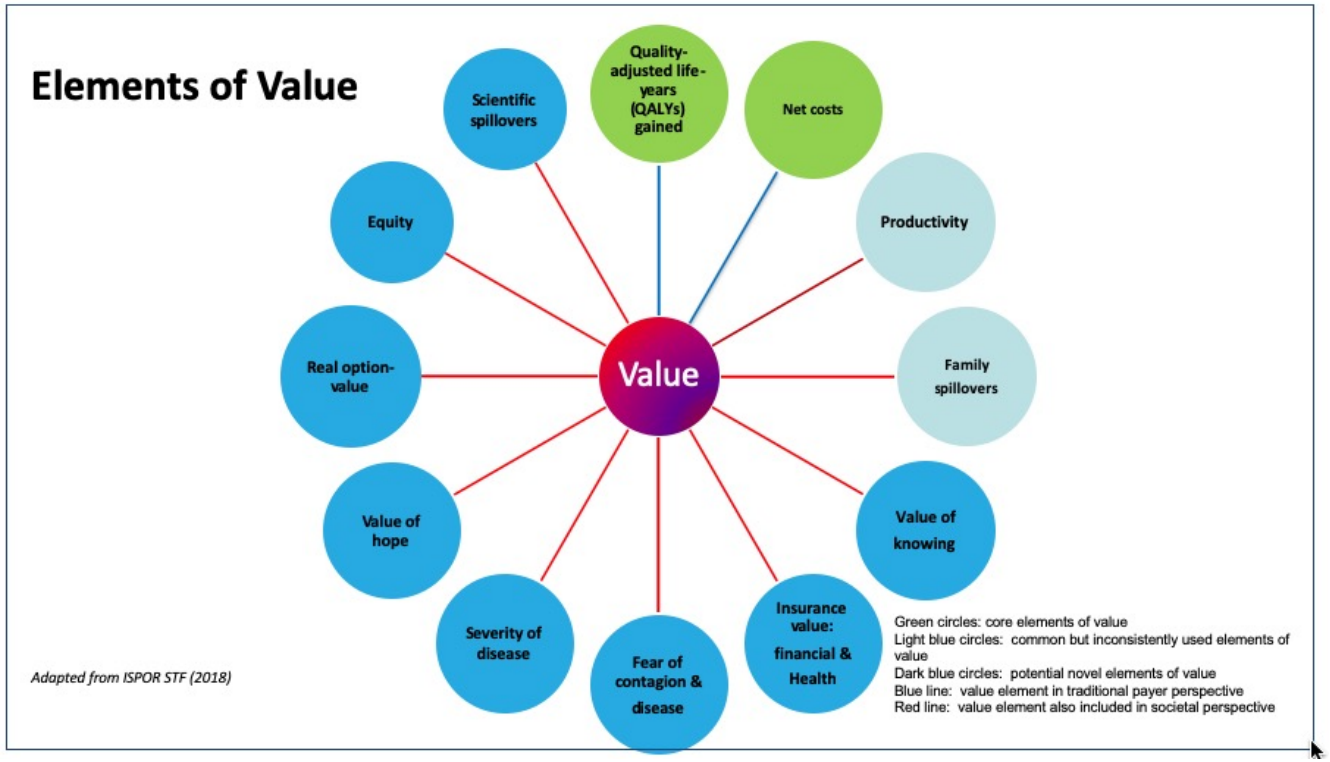
ISPOR Value Flower: Elements of Value to Consider in Assessing Gene-Targeted Therapies



Gene-targeted therapies can provide clinical and economic value by reducing uncertainty.

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Methodology

Hemophilia Gene Therapy Value Assessment: Methodological Challenges and Recommendations

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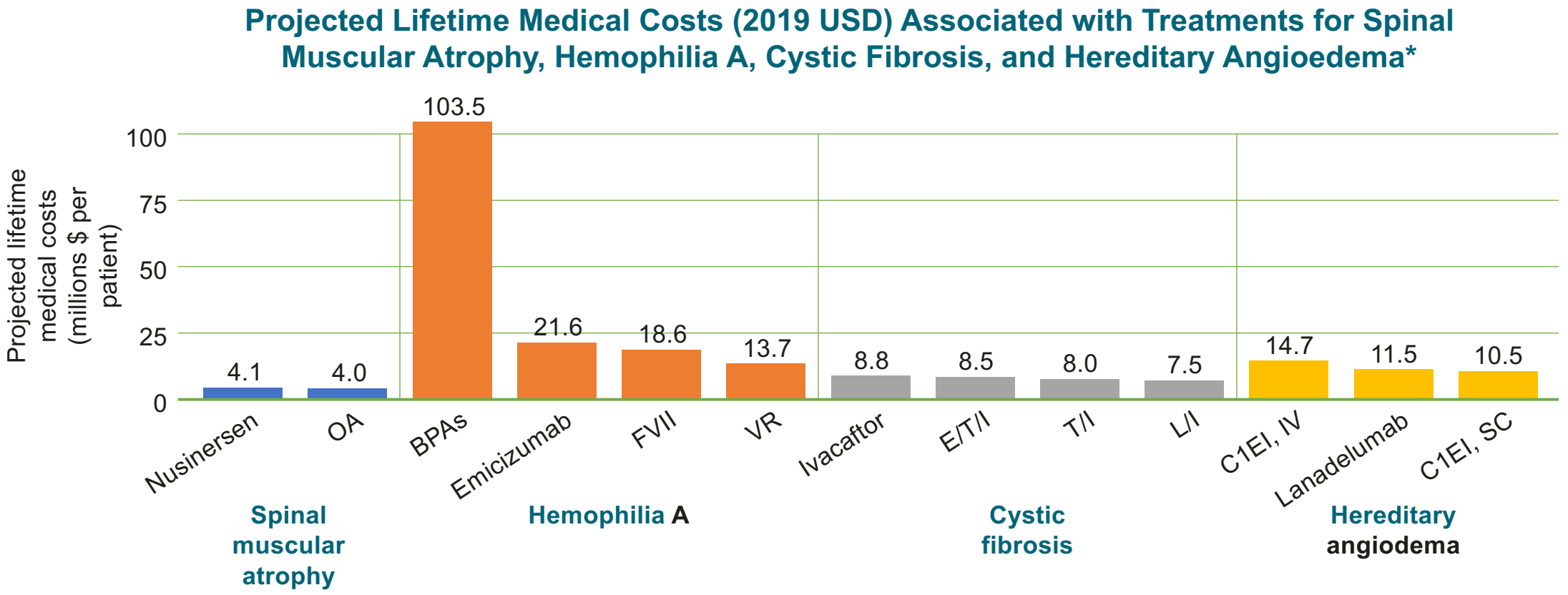
ABSTRACT

Six areas of methodological challenges

Figure 1. Key methodological challenges and recommendations. QOL indicates quality of life.

Key Methodological Challenges	Recommendations
1. **Immaturity of evidence and cure definition** • Limited follow-up data are currently available to assess the long-term benefits of hemophilia gene therapies • No consensus definition of cure in hemophilia	• Durability and cure assumptions should be assessed for each specific product based on clinical evidence, clinical input, and biological plausibility • Post-approval registry/real-world data should be collected to help address uncertainty when feasible
2. **Assessment of comparative effectiveness based on single-arm trials** • Clinical evidence for gene therapy in hemophilia are based on single-arm trials	• Synthetic historical control and lead in, self-controlled trial data should be considered in value assessment
3. **Important clinical and patient-centric outcomes** • Generic utility measures may not capture the true impact of hemophilia on QOL • Patient-centric outcomes beyond clinical outcomes are of high value in hemophilia	• Adding hemophilia-specific bolt-on questions to generic QOL instruments or by adjusting patient-reported values to those of the general population • CoreHem and patient-centric outcomes are valuable to assess
4. **Valuation of cost-offsets** • Large up-front cost with potential for substantial cost-offsets: to what extent should long-term cost-offsets be considered in assessing value?	• Cost-offset estimates should use real-world comparator costs
5. **Addressing value uncertainties** • Need to address price uncertainties ensuing from value uncertainties	• Outcome-based contracting should be explored to address price uncertainties ensuing from long-term outcomes uncertainties
6. **Perspectives of evaluation** • Gene therapy may impact indirect costs in addition to direct healthcare costs	• Both the healthcare system and societal perspective are valuable and should be presented together

Comparing Lifetime Medical Costs of Gene Therapies



Comparisons of the costs of gene therapies should take a patient's lifetime perspective.

BPA, bypassing agent; C1EI, C1 esterase inhibitor; E/T/I, elexacaftor/tezacaftor/ivacaftor (Trikafta); FVII, factor VIII; IV, intravenous; L/I, lumacaftor/ivacaftor;
OA, onasemnogene abeparvovec; SC, subcutaneous; T/I, tezacaftor/ivacaftor (Symdeko); USD, US dollar; VR, valoctocogene roxaparvovec.
Garrison LP et al. *J Manag Care Spec Pharm.* 2021;27(5):674-681.

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Recent Literature Summary—Elements Related to Uncertainty

PERSPECTIVES ON AUGMENTING COST-EFFECTIVENESS ANALYSES

Augmenting Cost-Effectiveness Analysis for Uncertainty: The Implications for Value Assessment—Rationale and Empirical Support

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FIGURE 1 Potential Elements of Value

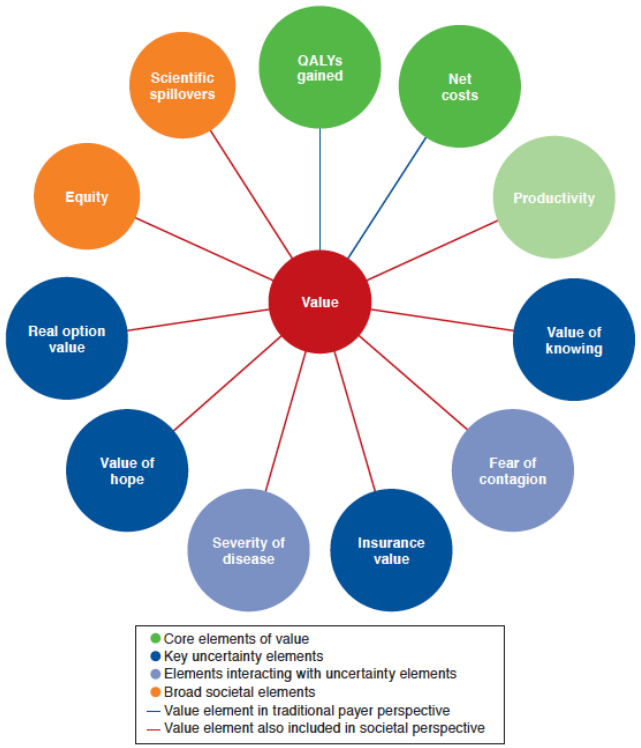
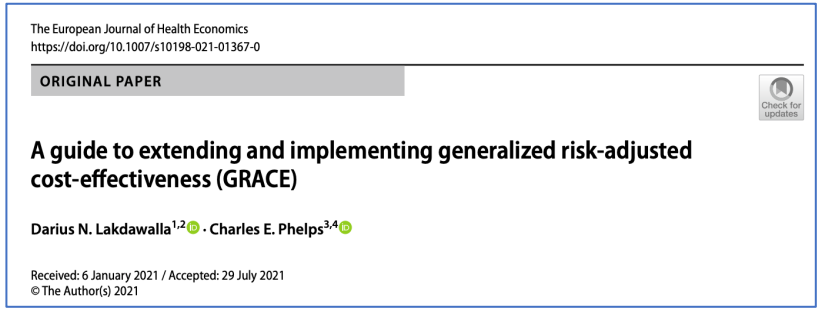


TABLE 1 Empirical Studies Relevant to the Measurement of Novel Uncertainty-Related Elements of Value

Element/Study	Context	Method	Monetary Effect Above Conventional ICER
Insurance value: financial risk protection			
Verguet et al., 2013[14]	Rotavirus-India (I) and Ethiopia (E)	Dynamic CEA modeling	Financial risk protection (FRP) of $16k (I) and $8K (E) per 1 million households. Largest FRP in lowest income quintile.
Verguet et al., 2015[15]	Tuberculosis in India	Universal public finance model (90% coverage)	Per million people in India, insurance value is $9,000, and 80% would accrue to the bottom 2 quintiles.
Insurance value: financial and physical health risk protection			
Shih et al., 2016[16]	Multiple sclerosis in United States	Parameterized utility function	33% of conventional value
Lakdawalla et al., 2017[10]	General U.S. population	Numerical exercise with a parameterized utility function	38%-62%: The physical insurance values greatly exceed the financial insurance value
Real option value			
Sanchez et al., 2012[17]	Small molecule medicine for chronic myeloid leukemia in United States	Projection of mortality trends	9% of conventional survival benefit
Snider et al., 2017[18]	Monoclonal antibody medicine for renal cell carcinoma and lung cancer in United States	Projection of mortality trends	5%-18% of conventional survival benefit
Li et al., 2019[19]	Monoclonal antibody medicine for metastatic melanoma in United States	Projection of mortality trends and new drug approvals and economic modeling	Incremental QALY gained increased by 5%-8% and ICER decreased by 0%-2%
Value of hope			
Lakdawalla et al., 2012[13]	Treatments for metastatic melanoma and metastatic breast cancer in United States	Discrete choice/contingent valuation	WTP $35,000 for a 1 standard deviation increase in survival
Shafrin et al., 2017[23]	Treatments for advanced stage melanoma or lung cancer in United States	Patient and physician surveys	Majority of patients prefer higher variance in survival; physicians do not
Shafrin et al., 2018[24]		Economic estimation	0.04 QALY
Value of knowing			
Neumann et al., 2012[25]	Predictive testing for diseases with no preventive option in United States	Stated-preference study	$109-$263 per test
Goldman et al., 2013[26] (Sood et al., 2013, technical analysis)[27]	Dx testing in personalized medicine: RA patients at risk for CV event on an NSAID in United States	Population economic modeling	Test generates $1,284 per patient

CEA = cost-effectiveness analysis; CV = cardiovascular; Dx = diagnostic; ICER = incremental cost-effectiveness ratio; NSAID = nonsteroidal anti-inflammatory drug; QALY = quality-adjusted life-year; RA = rheumatoid arthritis; WTP = willingness to pay.



". . . cost-effectiveness decision thresholds should be about 5 times higher for severe Alzheimer's disease than for peptic ulcer disease."

In my view: this framework is a pathbreaking advance.

The Generalized Risk-Adjusted Cost-Effectiveness (GRACE) Model

Lakdawalla-Phelps (2020a;b;c): Formal development of augmented CEA

Incorporates uncertainty and risk aversion:

- Variance in health outcomes
  - ➢ Not just mean effects
- Risk aversion for health outcomes
- Baseline severity of disease
- Likelihood of cures/value of hope

Implies →

- **Cost-effectiveness thresholds should vary, and they should be higher for rare, health-catastrophic diseases**
- Variance in outcomes generally reduces value, except for cures.

Conclusion:
Are our methods fit for purpose for gene therapies?

They provide a good starting point, but …

- We need to expand the concept and measurement of value to reflect:
  - The impact of baseline severity of disease on cost-effectiveness threshold
  - The impact of uncertainty on reducing value given health plan subscribers' risk aversion.

- We need to recognize a different role for real-world evidence before and after launch.

Thanks!

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