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

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.\(^1\)\(^2\)\(^3\)

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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:
Gene-targeted therapies can provide clinical and economic value by reducing uncertainty.
**Six areas of methodological challenges**

<table>
<thead>
<tr>
<th>Key Methodological Challenges</th>
<th>Recommendations</th>
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| 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 |
| 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  
• Outcome-based contracting should be explored to address price uncertainties ensuing from long-term outcomes uncertainties |
| 5. Addressing value uncertainties  
- Need to address price uncertainties ensuing from value uncertainties | • 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.

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<tr>
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<th>Spinal Muscular Atrophy</th>
<th>Hemophilia A</th>
<th>Cystic Fibrosis</th>
<th>Hereditary Angioedema</th>
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<td>Nusinersen</td>
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<td>OA</td>
<td>BPAs</td>
<td>Emicizumab</td>
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<td>VR</td>
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<td>C1EI, IV</td>
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<td>C1EI, SC</td>
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Projected Lifetime Medical Costs (2019 USD) Associated with Treatments for Spinal Muscular Atrophy, Hemophilia A, Cystic Fibrosis, and Hereditary Angioedema*

* 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.

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

Louis P. Garrison, Jr., PhD; Bernadita Zamora, PhD; Meng Li, PhD; and Adrian Towse, MSc, MPhil

Recent Literature Summary—Elements Related to Uncertainty

TABLE 1

<table>
<thead>
<tr>
<th>Element/Study</th>
<th>Context</th>
<th>Method</th>
<th>Monetary Effect Above Conventional ICER</th>
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<tbody>
<tr>
<td>Insurance</td>
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<td>Ayotz et al., 2013</td>
<td>Mexico (1) and Ethiopia (2)</td>
<td>Dynamic CEA modeling</td>
<td>Financial rate protection (FRP) of $1000 (10 and 360k) per 1 million households. Largest FRP in lowest income quintile</td>
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<tr>
<td>Ayotz et al., 2015</td>
<td>Tuberculosis in India</td>
<td>Universal public finance model (100% coverage)</td>
<td>Per million people in India, insurance value is $9,000, and 80% would accrue to the bottom 2 quintiles</td>
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| Real options |         |        |                                        |
| Sanchez et al., 2012 | Small molecule medicine for chronic kidney disease in United States | Projection of mortality trends | 9% of conventional survival benefit |
| Umeda et al., 2017 | Monoclonal antibody medicine for renal cell carcinoma and lung cancer in United States | Projection of mortality trends | 5%–10% of conventional survival benefit |
| Li et al., 2018 | 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%–3% |

| Value of hope |         |        |                                        |
| Laskis et al., 2013 | 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 |
| Shafrit et al., 2017 | 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 |
| Shafrit et al., 2018 | Economic estimates | DIS-CAH | QALY  |

| Value of knowledge |         |        |                                        |
| Neumann et al., 2014 | Predictive testing for diseases with no preventive option in United States | Stated preference study | $1000–$263 per test |
| Coldman et al., 2013 | DX testing in personalized medicine: RA patients at risk for CV event on an NSAID in United States | Population economic modeling | Test generates $1,384 per patient |

QALY—quality-adjusted life year; RA—rheumatoid arthritis; WTP—willingness to pay
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.

“In my view: this framework is a pathbreaking advance.”

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