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Gene Therapy Versus Common Care for Eligible Individuals With Sickle Cell Disease in the United States

A Cost-Effectiveness Analysis

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Background: Sickle cell disease (SCD) and its complications contribute to high rates of morbidity and early mortality and high cost in the United States and African heritage community.

Objective: To evaluate the cost-effectiveness of gene therapy for SCD and its value-based prices (VBPs).

Design: Comparative modeling analysis across 2 independently developed simulation models (University of Washington Model for Economic Analysis of Sickle Cell Cure [UW-MEASURE] and Fred Hutchinson Institute Sickle Cell Disease Outcomes Research and Economics Model [FH-HISCORE]) using the same databases.

Data Sources: Centers for Medicare & Medicaid Services claims data, 2008 to 2016; published literature.

Target Population: Persons eligible for gene therapy.

Time Horizon: Lifetime.

Perspective: U.S. health care sector and societal.

Intervention: Gene therapy versus common care.

Outcome Measures: Incremental cost-effectiveness ratios (ICERs), equity-informed VBPs, and price acceptability curves.

Results of Base-Case Analysis: At an assumed $2 million price for gene therapy, UW-MEASURE and FH-HISCORE estimated ICERs of $193 000 per QALY and $427 000 per QALY, respectively, under the health care sector perspective. Corresponding estimates from the societal perspective were $126 000 per QALY and $281 000 per QALY. The difference in results between models stemmed primarily from considering a slightly different target population and incorporating the quality-of-life (QOL) effects of splenic sequestration, priapism, and acute chest syndrome in the UW model. From a societal perspective, acceptable (>90% confidence) VBPs ranged from $1 million to $2.5 million depending on the use of alternative effective metrics or equity-informed threshold values.

Results of Sensitivity Analysis: Results were sensitive to the costs of myeloablative conditioning before gene therapy, effect on caregiver QOL, and effect of gene therapy on long-term survival.

Limitation: The short-term effects of gene therapy on vaso-occlusive events were extrapolated from 1 study.

Conclusion: Gene therapy for SCD below a $2 million price tag is likely to be cost-effective when applying a societal perspective at an equity-informed threshold for cost-effectiveness analysis.

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Sickle cell disease (SCD) is characterized by recurrent vaso-occlusion and hemolysis that contribute to acute episodes of pain, tissue ischemia, inflammation, and progressive organ damage (1). Approximately 100 000 people in the United States are living with SCD. More than 80% of those affected are of African heritage. Hydroxyurea has been a mainstay of therapy for decades but is underutilized. Although stem cell transplant offers a curative option, it is limited by a lack of genetically well-matched donors and other access challenges.

Genetic therapies that add nonsickling hemoglobin, increase fetal hemoglobin expression, or modify the sickle gene are in clinical trials and may soon be broadly available, but they are expected to be expensive, posing challenges for patients, insurers, and society (2, 3).

As part of the National Heart, Lung, and Blood Institute's Cure Sickle Cell Initiative (https://curesickle.org), 2 research groups independently developed simulation models to estimate costs and outcomes in SCD under different methods of care. Using those models, this work presents the cost-effectiveness of gene therapy in an eligible SCD population (4) compared with corresponding estimates under usual care in real-world settings, defined as common care (5).

See also:

Web-Only
Supplement

Common care included use of hydroxyurea and transfusions but excluded use of any other disease-modifying therapies or hematopoietic transplants. We discuss the potential value of such a gene therapy and value-based prices (VBPs) in SCD.

METHODS

Overview

The University of Washington Model for Economic Analysis of Sickle Cell Cure (UW-MEASURE) and the Fred Hutchinson Institute Sickle Cell Disease Outcomes Research and Economics Model (FH-HISCORE) simulated the progression of SCD under real-world–based care methods to estimate costs and outcomes over a lifetime from both the health care sector and societal perspectives (6) with and without gene therapy. The target population met published trial criteria from Medicaid and Medicare enrollees with SCD receiving common care. To facilitate comparison, the models used the same databases, patient populations, and model inputs (for example, quality-of-life [QOL] weights) whenever possible. Two models were independently constructed to determine whether making different choices for model structure and selection of specific SCD-related health states (based on some differences in recommendations for patients with SCD and other stakeholders) would affect the primary outcomes of the models. Both models' predictions incorporate important factors, such as demographics, vaso-occlusive events (VOEs), and the main chronic diseases. The UW model's progression incorporates an additional set of comorbidity conditions compared with the FH model. Therefore, when these models are applied to a curated eligible cohort of patients from the trial of LentiGlobin (bluebird bio; as described in the Discussion section) (4), the predictions generalize to a slightly different target population that we discuss in the Discussion section.

Study Cohort

Our primary data sets comprise claims data on the population of individuals with SCD enrolled in Medicaid, Medicare, or both from 2008 to 2016. The data sets included comprehensive information on use of office, outpatient, inpatient, emergency department, and home health care; durable medical equipment; long-term care; hospice services; and palliative care services (page 4 of the **Supplement**, available at Annals.org) for the following 3 insured cohorts: persons aged 18 to 100 years covered under Medicare fee-for-service, including those younger than 65 years with coverage due to disability; persons aged 0 to 64 years covered by Medicaid; and persons aged 0 to 100 years dually eligible for both Medicaid and Medicare. For details, see the conceptual modeling papers (5, 7). The analytic cohort applied published inclusion and exclusion criteria from SCD gene therapy trials (4) (**Supplement Table 5**, available at Annals.org).

Estimating Progression of SCD Under Common Care

Following best practice guidelines on model conceptualization and conceptual models as in other disease areas (8–11), SCD stakeholder inputs, and empirical data analyses, we developed conceptual models for the progression of SCD under current treatment practices (5, 7). The claims databases were used to estimate acute, subacute, and chronic outcomes of patients with SCD under common care (5) until death, disenrollment, or receipt of hematopoietic stem cell transplant (nongene therapy), whichever came first. Both models calibrated outcomes using split-sample methods (5, 7). **Table 1** compares the main features of these 2 simulation models.

UW-MEASURE

This microsimulation model follows individual patients annually, starting at any age, throughout their remaining lifetime and documents the incidence and continued prevalence of 6 chronic diseases (renal disease, pulmonary hypertension or cardiovascular disease, avascular necrosis, chronic lung disease, cognitive impairment, and ocular disease), 7 subacute conditions (mental disorder, asthma, chronic pain, leg ulcers, fatigue, liver complications, and sleep or breathing disorder), and 13 acute events (5). The 13 acute events include 4 types of severe VOEs—vaso-occlusive pain crisis (VOP), acute chest syndrome, acute splenic sequestration, and acute priapism—with the severity of VOEs based on lovo-cel (bluebird bio) trial definitions. Death was modeled annually. An illustration of UW-MEASURE is given in **Supplement Figure 4** (available at Annals.org), and other details on estimation are on pages 6 and 7 of the **Supplement**.

FH-HISCORE

This cohort simulation model follows cohorts of patients entering the model at any age and simulates follow-up biannually throughout their remaining lifetime. The model captures incident VOPs (0, 1, and ≥2); movement among VOP states over 6 months; and the incidence and continued prevalence of the following 4 chronic disease–related health states: cardiovascular disease–related conditions (stroke, myocardial infarction, pulmonary hypertension, and other cardiovascular complications), lung-related chronic conditions (asthma, chronic lung disease, and sleep apnea), chronic pain or fatigue, and chronic renal disease. Patients can die, with an estimated unique probability of death in each of the resulting 48 health states.

Calibration and Validation

Predicted outcomes from UW-MEASURE and FH-HISCORE matched those in the holdout sample (**Supplement Figures 8** to **16** and **23**, available at Annals.org).

Table 1. Overview of Simulation Models

Factor	UW-MEASURE	FH-HISCORE
Model features		
Type of model	Probabilistic microsimulation	Cohort-based probabilistic simulation
Data source	Population of individuals with SCD in the United States covered by CMS, 2008–2016	
Control treatment	Common care: empirical mix of hydroxyurea, transfusions, and no treatment	
Number of chronic and subacute conditions modeled	13 conditions (**Supplement Table 7**)	10 conditions, collapsed into 4 clusters
Number of acute conditions modeled	13 conditions (**Supplement Table 7**)	3 VOP states
Demographic factors considered	Age, biological sex, birth cohort indicators, CMS insurance type	Age
Lifetime epidemiology of comorbid conditions	41 distinct machine-learning models predicting next year's outcomes, for each insurance cohort	48 × 49 health state and mortality transition matrixes for each age decade
All-cause mortality	1 machine-learning model predicting mortality next year for each insurance cohort	48 × 49 health state and mortality transition matrixes for each age decade
Patient QOL model*	Min(non-VOE conditions) + 2 * Σ(losses from VOE)	Min(non-VOP conditions) + 2 * Σ(losses from VOP)
Family QOL (2 members)	2 * (1 − 0.25 * QOL loss for patient)	
Costs	All medical costs Net productivity and time costs Caregiver costs	All medical costs Net productivity Caregiver costs
Gene therapy–specific features		
Gene therapy target population	Application of trial-specific exclusion/inclusion criteria	
Gene therapy direct effects*	1. Administration effect on QOL 2. Effects on VOEs and their severity 3. No new chronic disease after 5 y (except cognitive impairment) 4. Long-term side effects 5. Achieve matched-sibling transplant survival with added uncertainty	1. Administration effect on QOL 2. Elimination of VOPs 3. No additional chronic diseases and associated survival benefits
Gene therapy costs	1. Drug price: $2 000 000 2. Administration costs 3. Cost of side effects 4. Other medical care costs	1. Drug price: $2 000 000 2. Administration costs 3. Other medical care costs

CMS = Centers for Medicare & Medicaid Services; FH-HISCORE = Fred Hutchinson Institute Sickle Cell Disease Outcomes Research and Economics Model; QOL = quality of life; SCD = sickle cell disease; UW-MEASURE = University of Washington Model for Economic Analysis of Sickle Cell Cure; VOEs = all vaso-occlusive events; VOPs = vaso-occlusive events due to pain crisis.
* VOEs are pain crisis, splenic sequestration, priapism, and acute chest syndrome.

Model Inputs

Efficacy, Safety, and Cost Associated With Gene Therapy

We considered the following 4 aspects of the effect of gene therapy.

Price. As a base case, both models consider an acquisition cost of $2 million, corresponding to other gene therapies involving genetically modified cells. We also derive potential value-based prices under different willingness-to-pay thresholds (3).

Administration. Associated costs include the transplant conditioning regimen before administration of the gene therapy, similar to the process required for autologous transplant (**Supplement Table 8**, available at Annals.org).

Efficacy. UW-MEASURE estimates the effect of gene therapy on all 4 types of VOEs as a mean relative risk (±SE) of 0.036 ± 0.20, based on outcomes from the lovo-cel trial (n = 25 with 6 to 36 months of follow-up) and doubles the variance of log relative risk beyond year 4 (4). It also assumes no hospital encounters from residual VOEs; assumes no hydroxyurea use, transfusion use, or their corresponding complications; halves utility decrement on residual VOEs (4); and stops the progression of chronic diseases after 5 years. It uses the established age- and sex-specific matched-sibling transplant survival curves under gene therapy using standard mortality ratios (12).

FH-HISCORE reduces the risk for VOPs to 0 after receipt of gene therapy. It also halts the progression of existing SCD-related chronic diseases immediately (instead of after 5 years as in UW-MEASURE) after receipt of gene therapy. Survival from that point reflects the existing burden of chronic disease (and not matched-sibling survival rates).

Adverse Effects. Myeloablative conditioning before gene therapy administration was assumed to have a mortality rate of 1% in year 1 in both models. UW-MEASURE considered the long-term effects of myeloablative conditioning on cognitive impairment and infertility (13–15) (**Supplement Table 9**, available at Annals.org).

Health State Utilities

Administration of gene therapy was associated with a utility decrement of 0.31 (loss of 3.7 months) in year 1 (16). Quality-of-life decrements for each condition

Table 2. Comparison of CMS Gene Therapy–Eligible Cohort With the Lovo-Cel Trial Cohort*

Characteristic	Lovo-Cel (bluebird bio) Trial (4) (n = 35)	Gene Therapy–Eligible Cohort (n = 4762)
Age		
Median (range), *y*	24 (12–38)	24 (12–38)
Distribution		
18–38 y	27 (77)	3646 (77)
12–17 y	8 (23)	1116 (23)
Female sex	13 (37)	2267 (48)
Race		
African heritage	34 (97)	3669 (77)
White	0 (0)	84 (2)
Hispanic	0 (0)	171 (4)
Other	0 (0)	62 (1)
Not provided	1 (3)	776 (16)
History of sickle cell disease		
Median annualized incidence of severe VOEs in 24 mo before enrollment (range)†	3.0 (0–13.5)	2.8 (1–12)
History of stroke	5 (14)	139 (3)
Hydroxyurea treatment ≤3 mo before study enrollment	23 (66)	1243 (26)
Chronic renal disease	–	958 (20)
Pulmonary hypertension or other cardiovascular complications	–	837 (18)
Avascular necrosis	–	1724 (36)
Chronic pain	–	2371 (50)
Liver complications	–	1154 (24)
Sleep/breathing disorders	–	1758 (37)
Acute anemia in past 12 mo	–	1483 (31)
≥1 chronic disease	–	3524 (74)
≥2 chronic diseases	–	3333 (70)
≥1 subacute condition	–	4476 (94)
≥3 subacute conditions	–	4095 (86)

CMS = Centers for Medicare & Medicaid Services; VOE = vaso-occlusive event.
* Values are numbers (percentages) unless otherwise indicated.
† Used a criterion of ≥2 diagnosed severe VOEs in the past 2 y, based on documented evidence of patients not seeking formal care for severe VOE for at least 50% of events (24). Note that the lovo-cel trial used a criterion of ≥4 severe VOEs in the past 2 y.

were derived from mapping Pediatric Quality of Life Inventory (PedsQL) data to the EuroQol Group 5-Dimension (EQ-5D) tool (17) and through a literature search (18) (**Supplement Tables 2** and **12**, available at Annals.org). For multiple conditions, both models used the minimum QOL from non-VOE conditions and then added utility losses from the VOEs modeled (VOPs only in FH-HISCORE) to determine the overall QOL. Both models doubled the utility losses from observed VOEs because at least half of VOEs do not result in care visits and yet have similar pain intensity (19). Both models summarized the QOL effects using quality-adjusted life-years (QALYs). UW-MEASURE additionally considers health years in total (HYTs) (20) because current laws explicitly prohibit the Centers for Medicare & Medicaid Services (CMS) from considering a health metric, such as the QALY, that "treats extending the life of an elderly, disabled, or terminally ill individual as of lower value than extending the life of an individual who is younger, nondisabled, or not terminally ill" (21). The HYT metric overcomes this issue (20) (pages 61 and 62 of the **Supplement**).

Direct Medical Costs

UW-MEASURE used unit costs for each type of health care use from CMS data stratified by insurance cohorts (**Supplement Table 3**, available at Annals.org). FH-HISCORE estimated the average total health spending per decade for each health state from the CMS data. All costs were inflated to 2021 U.S. dollars using the Personal Consumption Expenditures price index (6).

Time Uses and Productivity

UW-MEASURE relied on recently estimated, nationally representative mappings of QOL levels to different time uses (22) and valued productive time among persons aged 15 years or older through guidance provided by the Second Panel on Cost-Effectiveness in Health and Medicine (6) (**Supplement Table 3**).

For productivity, FH-HISCORE assumed that 25% of patients with SCD were employed before gene therapy, increasing to 75% after gene therapy (23).

Effects on Caregivers and Family Members

Both models captured QOL effects on caregivers and family members through losses in QOL for family members in proportion to the loss in QOL for the person with SCD and through time spent caring for patients with SCD (**Supplement Table 4**, available at Annals.org).

Analyses

Cost-effectiveness analysis examined the health care sector and societal perspectives, with lifetime

Table 3. Lifetime Comparative Pain-Related Outcomes Between SCD Gene Therapy and Common Care

Outcome	Mean Lifetime Events (±SE), *n*		Mean Absolute Difference in Count of Events (95% UI)
	SCD Gene Therapy (*n* = 4762)	Common Care (*n* = 4762)	
UW-MEASURE			
Acute pain crisis episodes	6.6 ± 32.7	92.8 ± 8.4	−86.2 (−157 to −17.3)*
Splenic sequestration	0.5 ± 9.75	1.4 ± 0.67	−0.9 (−20.2 to 18.4)
Priapism	0.9 ± 13.51	6.7 ± 3.30	−5.8 (−32.1 to 20.5)
Acute chest syndrome	4.1 ± 44.56	30.5 ± 11.86	−26.4 (−113 to 60.3)
FH-HISCORE			
Acute pain crisis episodes	0 ± 0	69.0 ± 0.87	−69.0 (−70.8 to −67.2)*

FH-HISCORE = Fred Hutchinson Institute Sickle Cell Disease Outcomes Research and Economics Model; SCD = sickle cell disease; UI = uncertainty interval; UW-MEASURE = University of Washington Model for Economic Analysis of Sickle Cell Cure.
* 95% UI excludes 0.

costs in 2021 U.S. dollars and QALYs for each treatment group as the primary outcomes. Future costs and outcomes were discounted at an annual rate of 3%. Sensitivity analyses were carried out on gene therapy–specific parameters. An impact inventory and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (24) are available in Supplement Tables 1, 13, and 14 (available at Annals.org).

VBPs

Both models evaluated alternative VBPs for gene therapy, indicating the maximum price (that is, acquisition cost of the drug product in the market) at which gene therapy remains cost-effective under different value thresholds.

We approached an equity-informed VBP to acknowledge disease severity and its disproportionate burden on patients and their family members, who mostly have African heritage. We converted a recent inequality aversion parameter (25) for this population to an estimate of an equity-informed threshold for cost-effectiveness analysis (26). Under this approach (Supplement Figure 21, available at Annals.org), we increased the acceptable cost-effectiveness thresholds of $100 000 per QALY (27) or $75 000 per HYT (20) by 50% to incorporate these equity concerns.

On the basis of the uncertainty around the VBP estimates from our probabilistic models, we present price acceptability curves indicating how likely the gene therapy is to be cost-effective at any given VBP.

The study, including the acquisition of deidentified Medicare and Medicaid claims data, was approved by the institutional review boards of the University of Washington and Fred Hutchinson Cancer Center.

Role of the Funding Source

The National Heart, Lung, and Blood Institute had no role in the study design; the collection, analysis, or interpretation of the data; or the decision to approve publication of the finished manuscript.

RESULTS

Population

Of the 50 970 patients identified (our most recent data), 4762 met inclusion and did not meet exclusion criteria, with 28 905 excluded because of age and 11 653 for having fewer than 2 diagnosed severe VOP events in the past 2 years (Supplement Table 5). Table 2 provides characteristics of this cohort compared with the lovo-cel trial population. All patients had at least 2 acute events (any of the 13 acute events) in the past 12 months (Supplement Table 7, available at Annals.org).

Effect of Gene Therapy on Pain

UW-MEASURE and FH-HISCORE predicted that gene therapy would reduce the lifetime number of acute pain crises by 86 and 69 events, respectively, versus common care (Table 3). UW-MEASURE also found that gene therapy may reduce other lifetime pain events—with considerable uncertainty, however.

Benefits of Gene Therapy Versus Common Care in Life Expectancy and Quality-Adjusted Metrics

For the gene therapy–eligible cohort of persons with SCD, both models projected improved outcomes with gene therapy versus common care in undiscounted life expectancy (17.4 years with UW-MEASURE and 17.0 years with FH-HISCORE), discounted QALYs (9.8 with UW-MEASURE [11.9 when including family benefits from gene therapy] and 5.1 with FH-HISCORE [5.4 when including family benefits]), and discounted HYTs (17.6 with UW-MEASURE [19.7 when including family benefits]) (Table 4 includes the 95% uncertainty intervals).

Note that the baseline undiscounted life expectancy differs between UW-MEASURE (13.4 years) and FH-HISCORE (19.6 years) because of differences in target populations and in the comorbid conditions incorporated into the 2 models.

Cost-Effectiveness Results

Table 4 presents the lifetime cost-effectiveness results from both models.

UW-MEASURE and FH-HISCORE estimated the total incremental health care costs, accounting for gene therapy drug price and administrative costs, to be $2 298 780 and $2 178 228, respectively. The incremental lifetime societal costs were estimated to be $1 498 971 and $1 568 094, respectively.

At a price of $2 million, the incremental cost-effectiveness ratios (ICERs) for gene therapy compared with common care from UW-MEASURE were $193 000 per QALY and $117 000 per HYT from the health care

Table 4. Lifetime Comparative Economic Outcomes Between Gene Therapy and Common Care

Average Lifetime Outcomes*	UW-MEASURE			FH-HISCORE		
	Mean (±SE)		Mean Difference (95% UI)	Mean (±SE)		Mean Difference (95% UI)
	Gene Therapy (n = 4762)	Common Care (n = 4762)		Gene Therapy (n = 4762)	Common Care (n = 4762)	
Life-years: patients						
Undiscounted	30.8 ± 3.7	13.4 ± 2.1	17.4 (10.5 to 24.3)†	36.6 ± 0.87	19.6 ± 0.26	17.0 (15.2 to 18.7)†
Discounted (3%)	18.1 ± 1.5	10.1 ± 1.1	7.9 (4.8 to 10.9)†	20.0 ± 0.32	13.7 ± 0.13	6.4 (5.7 to 7.0)†
QALYs: patients	12.4 ± 1.5	2.6 ± 0.3	9.8 (6.9 to 12.7)†	11.7 ± 0.39	6.6 ± 0.45	5.1 (4.7 to 5.9)†
HYTs: patients	30.5 ± 2.8	12.9 ± 1.3	17.6 (12.5 to 22.8)†	–	–	–
QALYs: family	18.2 ± 2.1	16.1 ± 1.8	2.1 (1.3 to 2.9)†	3.9 ± 0.20	3.5 ± 0.23	0.3 (−0.1 to 0.5)
QALYs: total	30.6 ± 2.9	18.7 ± 1.9	11.9 (8.5 to 15.3)†	15.6 ± 0.30	10.1 ± 0.25	5.4 (4.9 to 6.0)†
HYTs: total	48.7 ± 4.1	29.0 ± 3.0	19.7 (14.4 to 25.0)†	–	–	–
Medical costs, $	1 025 095 ± 222 737	1 197 111 ± 257 765	−172 065 (−766 366 to 422 304)	400 291 ± 12 887	668 136 ± 11 220	−267 872 (−298 304 to −235 470)†
Gene therapy drug costs, $	2 000 000	–	2 000 000	2 000 000	–	2 000 000
Gene therapy administration costs, $	470 796 ± 20 391	–	470 796 (430 830 to 510 762)†	470 089 ± 20 390	–	470 089 (430 830 to 510 762)†
Total medical costs, $	3 495 891 ± 224 097	1 197 111 ± 257 765	2 298 780 (1 702 334 to 2 895 226)†	2 846 391 ± 12 887	668 136 ± 11 220	2 178 228 (2 147 797 to 2 210 631)†
Productivity costs, $	−2 015 264 ± 202 808	−767 459 ± 104 590	−1 247 805 (−1 163 952 to −855 658)†	−1 313 829 ± 21 048	−298 451 ± 2791	−1 015 378 (−977 404 to −1 060 107)†
Patient time use costs, $	17 633 ± 17 315	46 253 ± 25 819	−28 620 (−85 380 to 28 140)	–	–	–
Caregiver time use costs, $	44 499 ± 13 732	63 534 ± 14 920	−19 035 (−52 587 to 14 517)	12 178 ± 302	37 581 ± 302	−25 402 (−26 702 to −24 530)†
Consumption costs, $‡	495 968 ± 98 488	–	495 968 (302 932 to 689 004)†	1 231 723 ± 19 732	839 398 ± 7851	392 324 (348 373 to 428 525)†
Total societal costs, $	2 038 410 ± 293 942	539 439 ± 241 109	1 498 971 (1 213 450 to 1 887 667)†	2 776 463 ± 12 337	1 246 691 ± 13 914	1 568 094 (1 532 272 to 1 590 646)†
ICER (health care)§	–	–	$193 000/QALY	–	–	$ 427 000/QALY
ICER (societal)§	–	–	$126 000/QALY	–	–	$ 281 000/QALY
ICER (health care)‖	–	–	$117 000/HYT	–	–	–
ICER (societal)‖	–	–	$ 76 000/HYT	–	–	–

FH-HISCORE = Fred Hutchinson Institute Sickle Cell Disease Outcomes Research and Economics Model; HYT = health year in total; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; UI = uncertainty interval; UW-MEASURE = University of Washington Model for Economic Analysis of Sickle Cell Cure.

* All outcomes are discounted at 3%, unless otherwise mentioned. All costs are in 2021 U.S. dollars.

† 95% UI excludes 0.

‡ UW-MEASURE considers only incremental consumption costs during extension of survival. FH-HISCORE reports consumption for all years, and then calculates incremental consumption.

§ Total incremental medical costs / total incremental QALYs; total incremental societal costs / total incremental QALYs.

‖ Total incremental medical costs / total incremental HYTs; total incremental societal costs / total incremental HYTs.

sector perspective and $126 000 per QALY and $76 000 per HYT from the societal perspective (Table 4).

The ICERs from FH-HISCORE were $427 000 per QALY from the health care sector perspective and $281 000 per QALY from the societal perspective (Table 4).

VBPs

UW-MEASURE estimated the societal VBP for gene therapy to be $1.7 million or $2.0 million using the traditional thresholds of $100 000 per QALY or $75 000 per HYT, respectively, and $2.3 million or $2.7 million using equity-informed thresholds. Accounting for uncertainty, we found a high (>95%) probability of acceptability for a gene therapy price of $2 million when using equity-informed thresholds. The confidence level of acceptability declined above an acquisition cost of $2.5 million (Figure 1, *top*).

FH-HISCORE estimated the societal VBP to be $1 million using a $100 000 per QALY threshold and $1.2 million using an equity-informed threshold (Figure 1, *bottom*).

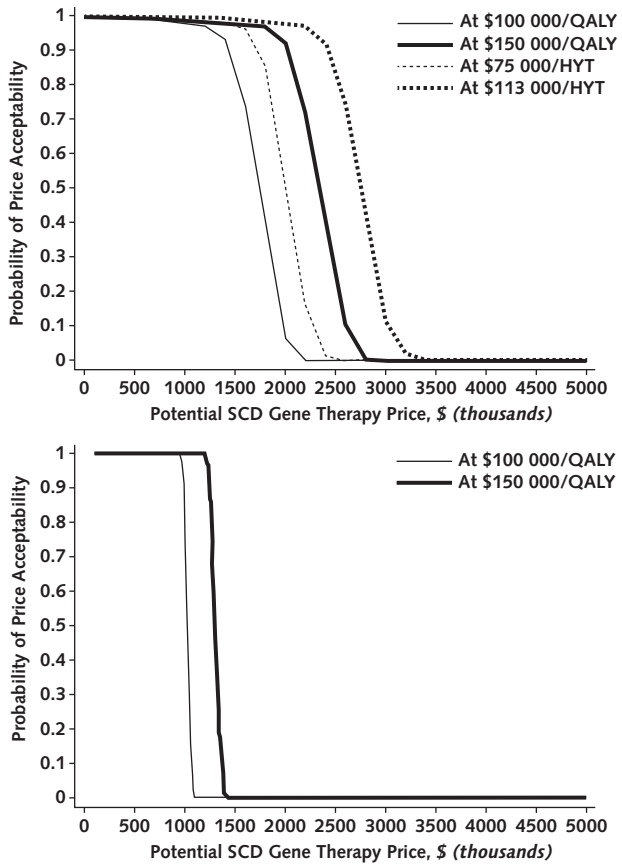
Sensitivity Analysis

Figure 2 shows a UW-MEASURE and FH-HISCORE sensitivity analysis of the value of gene therapy at a $2 million acquisition cost, using an equity-adjusted threshold and a societal perspective with respect to gene therapy–related parameters. The most sensitive parameters were the cost of gene therapy administration, effect on caregiver QOL, and effect of gene therapy on survival. An R-shiny platform for UW-MEASURE is available at uwchoice.shinyapps.io/measure.

DISCUSSION

Our 2 models suggest that gene therapy, compared with common care, could substantially improve life expectancy and QOL for persons with SCD who are insured under Medicare, Medicaid, or both and

Figure 1. Price acceptability curves for gene therapy for SCD.



The *x*-axis shows the potential value-based price (VBP) for gene therapy. The *y*-axis indicates the probability that the gene therapy is cost-effective at that VBP from a societal perspective. To compute VBPs, we considered both non–equity-based thresholds ($100 000/QALY or $75 000/HYT) and equity-informed thresholds ($150 000/QALY or $113 000/HYT). HYT = health year in total; QALY = quality-adjusted life-year; SCD = sickle cell disease. **Top.** University of Washington Model for Economic Analysis of Sickle Cell Cure (UW-MEASURE). **Bottom.** Fred Hutchinson Institute Sickle Cell Disease Outcomes Research and Economics Model (FH-HISCORE).

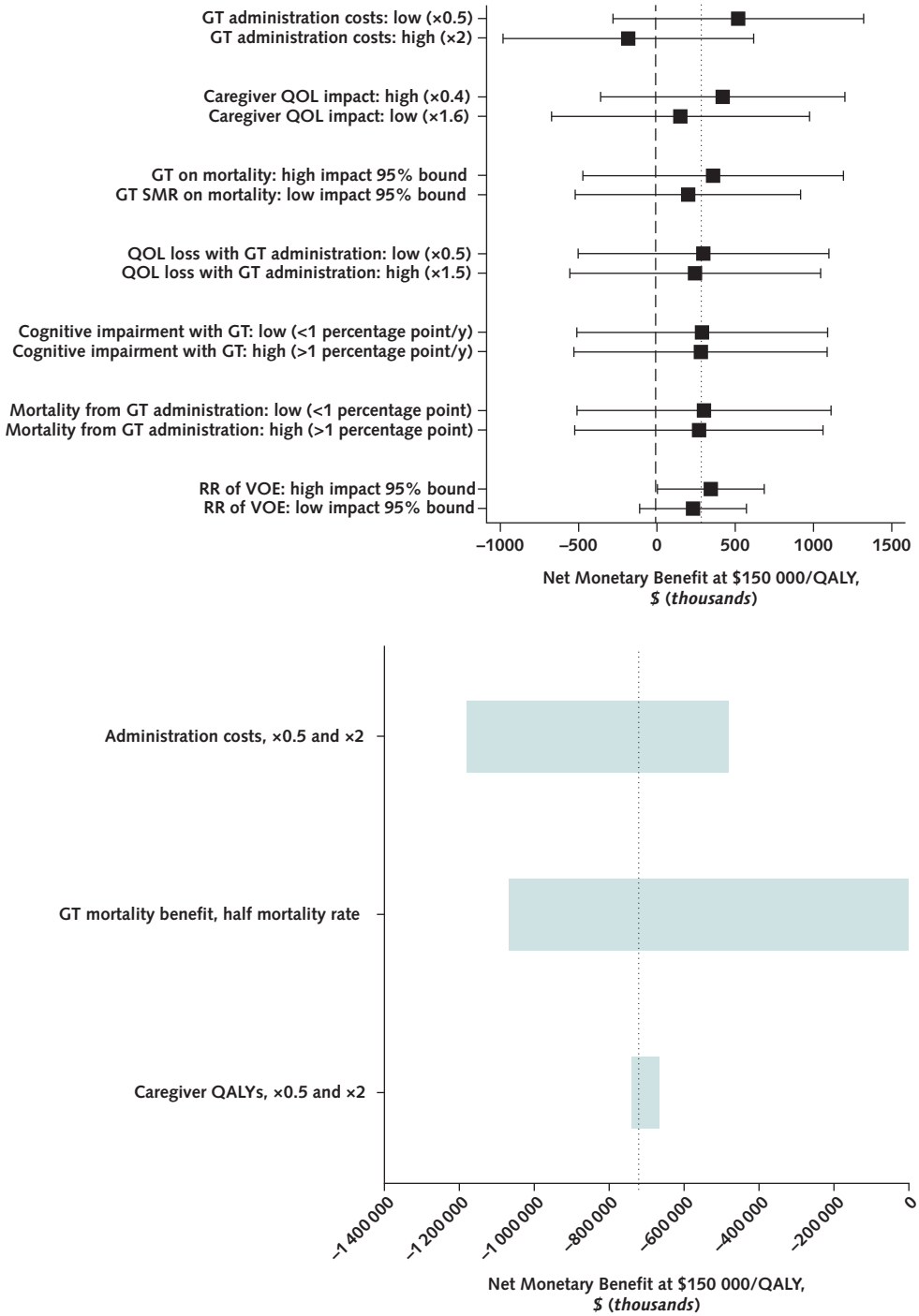
are eligible for current gene therapy protocols. Our analysis also found that gene therapy could be cost-effective for eligible individuals depending on comorbid conditions, types of pain events, and outcomes included in the analysis, as long as the price of gene therapy falls below $2 million based on a social perspective and an equity-adjusted threshold value for cost-effectiveness analysis. The ICERs were $126 000 per QALY and $281 000 per QALY from the societal perspective for the 2 models. Consequently, the acceptability of this upper limit of a VBP varied across the 2 models.

Our analyses provide detailed early evidence of such therapies' potential value and VBPs. The 2 models had several similarities in results, as well as some distinct differences. Both models projected fewer pain crisis events with gene therapy over the lifetime, which can offset the high upfront administration costs of gene therapy, greatly improve patients' prospects for long-term employment, decrease or possibly eliminate caregiver burden, and substantially improve recipients' life expectancy and recipients' and caregivers' QOL. Of note, gene therapy is less likely to be cost-effective at a price of $2 million from a health care sector perspective than from the broader societal perspective in both models. Unlike many other chronic conditions, SCD affects persons from an early age, such that their and their caregivers' life trajectories are dramatically different from those of peers without SCD. As such, from a societal perspective, both models show higher likelihood that the treatments will be cost-effective. One key difference between the models was their estimates for mean life expectancy under common care. This difference can be attributed to the target population for each model. Both models were run for the cohort of CMS patients eligible for gene therapy. The UW-MEASURE predictions of the evolving risks over a lifetime reflected a wider set of comorbid conditions that were part of the exclusion criteria. Hence, its results represented outcomes in a target population where the inclusion and exclusion criteria of the gene therapy trial were strictly adhered to. The FH-HISCORE predictions represented a more general gene therapy–eligible population, which is likely to align with the U.S. Food and Drug Administration labeling. Nevertheless, the comparative effectiveness of gene therapy in improving life expectancy was similar in both models. The estimates of QALYs under common care also differed between the 2 models, in part because of the difference in life expectancy estimates. In addition, the UW model included the effects of additional pain events, most importantly acute chest syndromes, which included additional disutility under common care.

The Institute for Clinical and Economic Review reported estimates of the ICERs (about $162 000 per QALY from a societal perspective) for gene therapies in this population that fall between the estimates from UW-MEASURE and FH-HISCORE (28). Another study evaluated the cost-effectiveness of a hypothetical cell or gene therapy cure compared with the standard of care in this population (29). Their estimate of the ICER from the health care sector perspective was the lowest but was closer to that of UW-MEASURE.

Our models have several strengths. First, we empirically estimate survival for patients with SCD. Second, we consider and empirically estimate the burden of acute and chronic conditions for patients with SCD, accounting for the co-occurrence of conditions and the role of aging. Third, the models are sensitive to a patient's baseline health conditions before receiving gene therapy. Both simulation models (UW-MEASURE and FH-HISCORE) were validated by comparing their predicted estimates of complications and mortality against those observed in the CMS database.

Figure 2. One-way sensitivity analysis for the net monetary benefit of SCD GT, from a societal perspective, with respect to GT-specific parameters.



Net monetary benefit is calculated as (incremental QALYs * [150 000/QALY] − incremental costs). 150 000/QALY is the equity-informed threshold for cost-effectiveness analysis. Net monetary benefit >0 favors gene therapy. GT = gene therapy; QALY = quality-adjusted life-year; QOL = quality of life; RR = risk ratio; SCD = sickle cell disease; SMR = standard mortality rate; VOE = vaso-occlusive event. **Top.** University of Washington Model for Economic Analysis of Sickle Cell Cure (UW-MEASURE). Base net monetary benefit = $286 000 (*vertical dotted line*), indicating positive value for a $2 million gene therapy at $150 000/QALY; sensitivity analysis shows changes in mean net monetary benefit values (and 95% CI) with low or high parameter values. **Bottom.** Fred Hutchinson Institute Sickle Cell Disease Outcomes Research and Economics Model (FH-HISCORE). Base net monetary benefit = −$758 000 (*vertical dotted line*), indicating negative value for a $2 million gene therapy at $150 000/QALY; sensitivity analysis shows changes in mean net monetary benefit values with low or high parameter values.

There are several limitations to our modeling efforts of SCD, a highly complex condition with numerous serious comorbid conditions. We did extensive internal validations on both models, which can improve confidence that the predicted outcomes closely approximate what would be expected over time for patients meeting eligibility criteria for gene therapy. However, a key model issue is the assumption that the efficacy of gene therapy will persist beyond 36 months. Billing code inaccuracies and problems with systematic upcoding for resource use exist in both models. Acute coronary syndrome events and VOPs, the 2 main outcome targets, seem to be coded accurately in claims data (30). Other comorbid conditions, such as infections or dactylitis, may not be coded as accurately. Because the UW model considers a larger number of acute and chronic conditions, it is likely to be more susceptible to these coding errors, although the direction of bias remains unclear. The UW model also predicts the incidence of future comorbid conditions with gene therapy using the same prediction models as under common care, but muting the effects of VOEs and chronic conditions, thereby overstating their incidence. This likely will make our cost-effectiveness and VBP estimates conservative. A decision maker can consider other social and distributional issues to further shape the VBPs (26).

Both models found that the effect of gene therapy on mortality was one of the top sensitive parameters. The benefit duration is among the primary uncertainties surrounding gene therapy that will most affect its cost-effectiveness. This issue is particularly important because only 1 gene therapy trial ($n = 25$) has reported outcomes, with a median follow-up of 17.3 months (range, 3.7 to 37.6 months). As longer-term follow-up results are presented for more patients in the early trials, and results from different gene therapies are reported, it will be important to compare results predicted here with those observed and reevaluate value as needed.

Future work comparing the clinical and economic effect of gene therapy versus stem cell transplantation will assist decision makers in guiding patients to the most appropriate and cost-effective therapy. Our results suggest that gene therapy for SCD can bring substantial benefits to this population and provide evidence for the proper reimbursement level for these therapies by CMS.

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