Preimplantation genetic testing for sickle cell disease: a cost-effectiveness analysis

Joshua C. Combs, M.D.,[a,b] Maura Dougherty, M.S.,[e] Meghan U. Yamasaki, D.O.,[a,b] Alan H. DeCherney, M.D.,[a] Kate M. Devine, M.D.,[c] Micah J. Hill, D.O.,[a,b] Erin Rothwell, Ph.D.,[d] Jeanne E. O'Brien, M.D.,[c] and Richard E. Nelson, Ph.D.[d]

[a] Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, Maryland; [b] Walter Reed National Military Medical Center, Bethesda, Maryland [c] Shady Grove Fertility Center, Rockville, Maryland; [d] University of Utah School of Medicine, Salt Lake City, Utah; [e] University of Utah, Salt Lake City, Utah

Objective: To evaluate the cost-effectiveness of in vitro fertilization with preimplantation genetic testing for monogenic disease (IVF + PGT-M) in the conception of a nonsickle cell disease (non-SCD) individual compared with standard of care treatment for a naturally conceived, sickle cell disease (SCD)-affected individual.
Design: A Markov simulation model was constructed to evaluate a one-time IVF + PGT-M treatment compared with the lifetime standard of care costs of treatment for an individual potentially born with SCD. Using an annual discount rate of 3% for cost and outcome measures, quality-adjusted life years were constructed from utility weights and life expectancy values and then used as the effectiveness measurement. An incremental cost-effectiveness ratio was calculated for both treatment arms, and a willingness-to-pay threshold of $50,000 per quality-adjusted life year was assumed.
Setting: Tertiary care or university medical center.
Patient(s): A hypothetical cohort of 10,000 patients was analzyed over a lifetime horizon using yearly cycles.
Intervention(s): In vitro fertilization with preimplantation genetic testing for monogenic disease use in conception of a non-SCD individual.
Main Outcome Measure(s): The primary outcomes of interest were the incremental cost and effectiveness of an IVF+PGT-M conception compared with the SOC treatment of an SCD-affected individual.
Result(s): In vitro fertilization with preimplantation genetic testing for monogenic disease was the optimal strategy in 93.17% of the iterations. An incremental savings of $137,594 was demonstrated with a gain of 1.96 QALYs and 3.69 life years over a lifetime. Sensitivity analysis demonstrated that SOC treatment never met equivalent cost-effectiveness.
Conclusion(s): Our model demonstrates that IVF + PGT-M for selection against SCD, compared with lifetime SOC treatment for those affected, is the most cost-effective strategy within the United States healthcare sector. (Fertil Steril Rep® 2023;4:300–7. ©2023 by American Society for Reproductive Medicine.)
Key Words: Cost, sickle cell disease, PGT-M

Sickle cell disease (SCD) is an autosomal recessive hemoglobinopathy affecting approximately 100,000 Americans, with vastly more affected across the globe (1, 2). Each year, roughly 2,000 newborns are diagnosed with this disease, which has become the most inherited and preventable blood disorder in the United States (3). A consistent single nucleotide substitution results in hemoglobin S, which can become misshapen, or sickled, when deoxygenated (2). This malformation leads to vaso-occlusive events, hemolytic anemia, inflammation, hypercoagulability, and vasculopathy, which may result in an array of sequelae ranging from pain crises, chronic infections, stroke and thromboembolic events, heart failure, acute chest syndrome, and even permanent organ damage, often shortening one's life expectancy by decades (2, 4–6). Treatment may include prophylactic antibiotics and vaccinations for infection prevention,

Received February 21, 2023; revised and accepted June 8, 2023.
J.C.C. has nothing to disclose. M.D. has nothing to disclose. M.U.Y. has nothing to disclose. A.H.D. has nothing to disclose. K.M.D. has nothing to disclose. M.J.H. has nothing to disclose. E.R. has nothing to disclose. J.E.O.B. has nothing to disclose. R.E.N. has nothing to disclose.
Supported in part by the Utah Center for Excellence in ELSI Research (UCEER). UCEER is supported by the National Human Genome Research Institute of the National Institutes of Health under RM1HG009037. The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or U.S. Government.
Correspondence: Joshua C. Combs, M.D., Eunice Kennedy Shriver National Institute of Child Health and Human Development, 9000 Rockville Pike, Bethesda, Maryland, 20892 (E-mail: joshuacombs@hotmail.com).

Fertil Steril Rep® Vol. 4, No. 3, September 2023 2666-3341

https://doi.org/10.1016/j.xfre.2023.06.001

opioids and analgesics for pain control, disease-modifying drugs such as hydroxyurea, as well as blood and exchange transfusions. Although curative therapies exist, they do not come without major limitations and risks. Hematopoietic stem cell transplant is one option, however, is typically reserved for severe cases. Gene therapies now offer novel curative options but remain investigational at this time. When the diagnosis of SCD is made in utero, termination of the affected pregnancy can serve as a preventative therapy; however, this option may not be acceptable to all patients and may be limited by state law.

Although SCD is most prevalent in individuals of African descent, it is also commonly seen in those of Hispanic, Greek, Italian, Turkish, Arabic, Iranian, Central and South American, and Asian Indian descent (2, 4). For those of African or Hispanic descent, approximately 1 per 365 live births and 1 per 16,300 live births will be affected by the disease, respectively (7). Diagnosis is most commonly made using hemoglobin electrophoresis or, more recently, through carrier screening using next-generation sequencing. Although older guidelines recommended a race-based screening approach, the American College of Obstetricians and Gynecologists now encourages universal hemoglobinopathy testing of all individuals considering pregnancy or at the time of initial prenatal visit (8). The American College of Medical Genetics also endorses pan-ethnic carrier screening for more than 100 conditions, including SCD (9).

When known carriers or affected individuals wish to conceive, they have the option of utilizing in vitro fertilization (IVF) with preimplantation genetic testing for monogenic disorders (PGT-M) to ensure that their offspring do not express the disease. Contemporary PGT involves obtaining 5–10 cells of the trophectoderm of a blastocyst embryo before vitrification with subsequent analysis of the amplified DNA. The amplified DNA is then analyzed using next-generation sequencing platforms or single nucleotide polymorphism arrays (10). On the basis of the results, unaffected embryos are preferentially selected for future transfer. Interestingly, preimplantation genetic testing for aneuploidy (PGT-A) is often performed concurrently with PGT-M, thus allowing preferential transfer of unaffected, euploid embryos. Although utilization of PGT-M with PGT-A results in fewer available embryos for transfer (11), one study found that use of both resulted in lower miscarriage and higher implantation and live birth rates compared with PGT-M alone (12).

Given the potential impact of disease on an individual, their family, and the healthcare system, the question of why high-risk couples would not use such technological advancements to ensure their offspring do not express the disease arises. A study by Nickel et al. (13) reported that only 24% of at-risk parents with a SCD child were aware of PGT-M. A key factor in the decision-making process is likely the cost associated with IVF and PGT, with several sources quoting a cost of $30,000 or more to have an unaffected live birth (14–17). Although this is a significant cost burden, one must wonder how this cost compares with the overall lifelong healthcare cost of caring for an individual with SCD.

To provide insight into these questions, we sought to perform a cost-effectiveness analysis comparing the cost of disease prevention via IVF + PGT-M to the cost of care for an individual with SCD. We hypothesized that prevention of SCD-affected offspring through the use of IVF + PGT-M was more cost-effective than lifelong treatment of an individual with SCD.

MATERIALS AND METHODS

Study Design

We constructed a Markov simulation model to evaluate the cost-effectiveness of a one-time PGT-M treatment compared with the lifetime standard of care (SOC) costs of treatment for an individual potentially born with SCD. For bimodal cost comparison, disease prevention via pregnancy termination was not included in the nonintervention arm. The Markov model was analyzed using a hypothetical cohort of 10,000 patients analyzed over a lifetime time horizon using yearly cycles and an annual discount rate of 3% for both the cost and health outcome measures. Given the hypothetical nature of the cohort studied, no Institutional Review Board approval was required. The primary outcomes of interest were the incremental cost and incremental effectiveness between IVF + PGT-M compared with the SOC treatment of a SCD-affected individual. Strategy dominance was assigned to the intervention, which proved to be less costly and clinically superior. The costs of treatment were considered comprehensive in both arms, and the effectiveness of treatment was measured using the quality-adjusted life year (QALY). We parameterized our model with inputs obtained from published literature and ran our analysis using base-case values for each parameter. The robustness of the results obtained was then explored using both deterministic and probabilistic sensitivity analyses.

Model

The Markov model was conducted in TreeAge Healthcare Pro 2022 (TreeAge Software LLC, Williamstown, MA). Couples were placed into one of two arms on the basis of whether they underwent IVF + PGT-M or not. In each arm, genetic carrier screening for SCD during the preconception state was conducted with a 50% probability to simulate real-world screening uptake. In the treatment arm, IVF + PGT-M was used to preferentially select a nonSCD-affected embryo in a one-time process assumed to be 100% effective in ruling out disease. In the comparison arm, the couple was presumed to have conceived naturally with a 25% risk of SCD transmission on the basis of heterozygous carrier status of an autosomal recessive disease for both parents. It was assumed that SCD could only develop at birth, allowing for no chance of remission for an individual initially born without the disease. Sickle cell disease was characterized by year as either mild, moderate, or severe, and individuals with the disease could transition between different severity levels each year in the model. The individual could also move to the death state at the end of any year from any SCD or nonSCD state, on the basis of the probability of mortality for each case. Death was considered an absorbing state.

Transition Probabilities

The probability of mortality with each cycle was obtained from simulated life tables for African American individuals created from the mortality rates listed in the Centers for Disease Control and Prevention National Vital Statistics Wonder Database (18). We used African-American-specific mortality data because this disease is particularly prevalent in this population. The mortality probabilities are listed in Supplemental Table 1 (available online).

For individuals who did not undergo IVF + PGT-M, the probability of being born with SCD was calculated on the basis of the assumption that both parents were known carriers of SCD. When not born with SCD, the patient either remained in the standard state of health for an individual without SCD or died. The mortality probabilities were drawn from the same source as described above. The probability of being born into each level of SCD severity was obtained from real-world data measuring the distribution of patients <10 years of age in each stage (19).

The probability of mortality at the end of each cycle was the same regardless of the individual's current stage of disease. The mortality probabilities were obtained from a study by Paulonikis et al. (20) and had mortalities separated by 10-year age intervals for ages 5–74 years old, with separate mortality probabilities for those aged 0–4 and ≥75 years. These mortality probabilities are listed in Supplemental Table 1.

The probabilities of transitioning between stages of SCD were calculated using the ordered logit transition probability regression coefficients listed by Salcedo et al. (19) using methods suggested by Jung (21). The coefficients used in this method were a weighted average of the gender-specific coefficients to match the demographics of the patient cohort analyzed by Salcedo et al. (19). This was done to estimate the probability of transition, regardless of gender, which was not controlled for in this analysis. The cut-point coefficients were assumed to refer to the moderate and severe states and were included in the calculation of the probability of those transitions.

Costs

The costs were analyzed from a public-payer perspective. The yearly cost of SOC treatment was obtained from Alemayehu and Warner (22) 2004, with the range of costs determined using the lowest and highest yearly costs of care listed. Yearly, severity level-specific costs for SCD treatment were calculated using the weighted average of the regression coefficients from gender-stratified generalized linear models with gamma distributions provided by Salcedo et al (19). These coefficients were generated using data from a sample of individuals with SCD from a large commercial claims database between 2007 and 2017. These treatment costs included all antibiotics, vaccinations, pain-relief medications, hydroxyurea, blood transfusions, and stem cell transplants. The costs associated with each severity level were then calculated by exponentiating the sum of these regression coefficients relevant to each level.

The cost of the IVF + PGT-M strategy was derived from an aggregate of published sources and included stimulation medications, monitoring, oocyte retrieval, fertilization, PGT analysis, vitrification, and embryo transfer (15–17, 23–28). To account for the potential need for multiple embryo transfer events to reach live birth, the cost of live birth was determined by multiplying the chance of success by the cost of each successive attempt, assuming a maximum number of three attempts. Pertransfer and cumulative live birth rates for up to three single euploid transfers were derived from Pirtea et al. (23), in which all included patients were between the ages of 18 and 45 years, had a body mass index of >18 kg/m^2 and <40 kg/m^2, and had a morphologically normal uterus on saline sonography and/or hysteroscopy. The costs of natural conception, live birth, and death were assumed to be zero.

All cost input parameters except for the costs of SOC for individuals with SCD are included in Table 1 (29). All costs were adjusted to 2021 US dollars using the Consumer Price Index and discounted at a 3% annual rate. The costs associated with genetic screening for SCD were taken from Quest Diagnostics' published pricing lists.

Health Outcomes

The measure of effectiveness used in the model was the QALY, constructed by weighing the time spent in different health states by a utility value that varied from 0 (death) to 1 (perfect health). Health states included nonSCD, SCD, or death. Age-specific utilities for the nonSCD health state were taken from Jiang et al. (29), whereas age-specific SCD utilities were obtained from Lubeck et al. (30). These utilities were assumed to be the same regardless of the disease stage. The utility of death was assumed to be zero. All utility values are listed in Table 1. Similar to costs, future QALYs were discounted at a 3% annual rate.

Sensitivity Analyses

We conducted deterministic sensitivity analyses in which each input parameter was varied individually. Each variance was conducted according to intervals reported in the literature, by ± 20% for costs when no literature value was reported, and between 0 and 1 for all utilities, transition, and mortality probabilities. In addition, we also conducted two probabilistic sensitivity analyses (PSAs) using 10,000 Monte Carlo simulations. Cost parameters were assumed to have a gamma distribution, and probabilities and utilities were assumed to have beta distributions. The first PSA varied all utilities, transition probabilities, and cost parameters by ±20% of their mean value. The second PSA continued to vary the utilities and transition probabilities by ±20% but varied the cost parameters by ±75% to account for a wide range of potential health costs.

RESULTS

Base Case and Alternative Scenario Results

As shown in Table 2, PGT-M yielded more QALYs at a lower cost compared with the no PGT-M strategy for the base-case

TABLE 1

Model input parameters.

Parameter	Value	Source
Costs (2021 USD)		
IVF + PGT-M cost to live birth	$29,609	Neal et al. (15) 2018, Crawford et al. (16) 2016, Lipton et al. (17) 2020, Pirtea et al. (23) 2021, Katz et al. (24) 2010, Wu et al. (25) 2014, Bakkensen et al. (26) 2022, Khorshid et al. (27) 2023, Facadio et al. (28) 2021
Natural conception cost to live birth	$0	Model assumption
Yearly nonSCD SOC care	$6,074	Alemayehu and Warner (22) 2004
Genetic screening for SCD	$45	Quest diagnostics
Probabilities		
Incidence of SCD	0.25	Model assumption (both parents SCD carriers)
Mild SCD	0.50	Salcedo et al. (19) 2021
Moderate SCD	0.22	Salcedo et al. (19) 2021
Severe SCD	0.28	Salcedo et al. (19) 2021
Genetic SCD carrier screening	0.50	Model assumption
Utilities		
Individuals with SCD aged 1–18 y	0.69	Salcedo et al. (19) 2021
Individuals with SCD aged 19–100 y	0.68	Salcedo et al. (19) 2021
Individuals without SCD aged 1–24 y	0.919	Jian, Janssen, and Pickard 2021
Individuals without SCD aged 25–34 y	0.911	Jian, Janssen, and Pickard 2021
Individuals without SCD aged 35–44 y	0.841	Jian et al. (29) 2021
Individuals without SCD aged 45–54 y	0.816	Jian et al. (29) 2021
Individuals without SCD aged 55–64 y	0.815	Jian et al. (29) 2021
Individuals without SCD aged 65–74 y	0.824	Jian et al. (29) 2021
Individuals without SCD aged 75–100 y	0.811	Jian et al. (29) 2021

IVF = in vitro fertilization; PGT-M = preimplantation genetic testing for monogenic and single gene disorders; SCD = sickle cell disease; SOC = standard-of-care.

Combs. Cost effectiveness of PGT for sickle cell. Fertil Steril Rep 2023.

analysis, which assumed 25% of carrier-parent natural conceptions developed SCD. In vitro fertilization with preimplantation genetic testing for monogenic disease was both less costly ($201,676 vs. $339,270) and more effective (26.22 QALYs vs. 24.26 QALYs) compared with lifetime SCD SOC treatment.

Deterministic Sensitivity Analyses

As shown in Figure 1, the results of the one-way sensitivity analyses indicate that our model's results were most sensitive to the SOC cost for mild SCD, however, the IVF+PGT-M strategy was still cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY, even at the high-end value ($75,000) of the range for this parameter. Other parameters that had a significant impact on the results included the yearly probability of mortality for individuals with SCD, the probability of transition from mild to severe SCD, and the initial probabilities of being in the mild and severe levels of SCD.

Probabilistic Sensitivity Analysis

The results from the PSA are shown as a scatterplot on the cost-effectiveness plane in Figure 2. At a WTP threshold of $50,000 per QALY, IVF + PGT-M was the optimal strategy in 93.17% of the iterations. Iterations that were not dominant were largely because of extreme and likely unrealistic values for the utilities in individuals with and without SCD, yearly mortality values for individuals with SCD, and yearly SOC costs for individuals without SCD. Results were similar when we allowed input parameters to vary by 75%.

TABLE 2

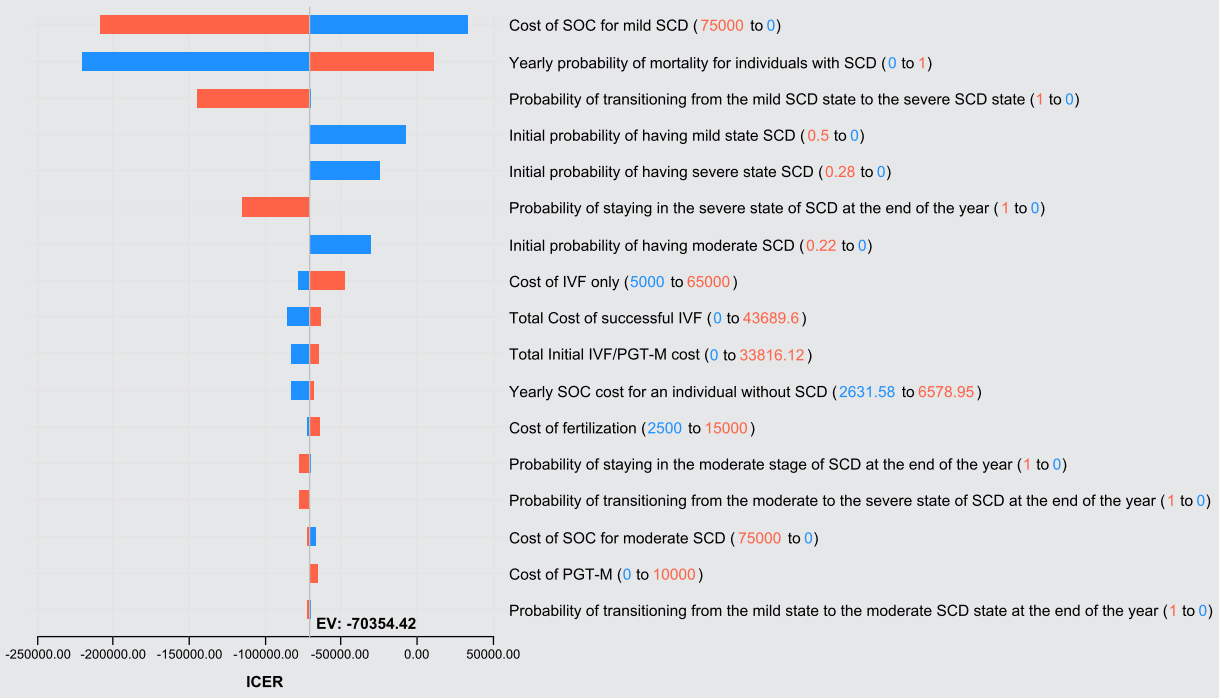
Cost-effectiveness analysis results.

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	LYs	Incremental LYs	ICER
No PGT-M	339,270	-	24.26		72.71		-
PGT-M	201,676	-137, 594	26.22	1.96	69.02	3.69	Dominant

ICER = incremental cost-effectiveness ratio; LY = life year; PGT-M = preimplantation genetic testing for monogenic and single gene disorders; QALY = quality-adjusted life year; SCD = sickle cell disease.

Combs. Cost effectiveness of PGT for sickle cell. Fertil Steril Rep 2023.

FIGURE 1



Tornado diagram showing results from one-way sensitivity analyses. IVF = in vitro fertilization; PGT-M = preimplantation genetic testing for monogenic and single gene disorders; SCD = sickle cell disease; SOC = standard-of-care. *Note*: The blue portion of the bars represents lower values of the parameter and the red portions indicate a higher value for that parameter.

Combs. Cost effectiveness of PGT for sickle cell. Fertil Steril Rep 2023.

DISCUSSION

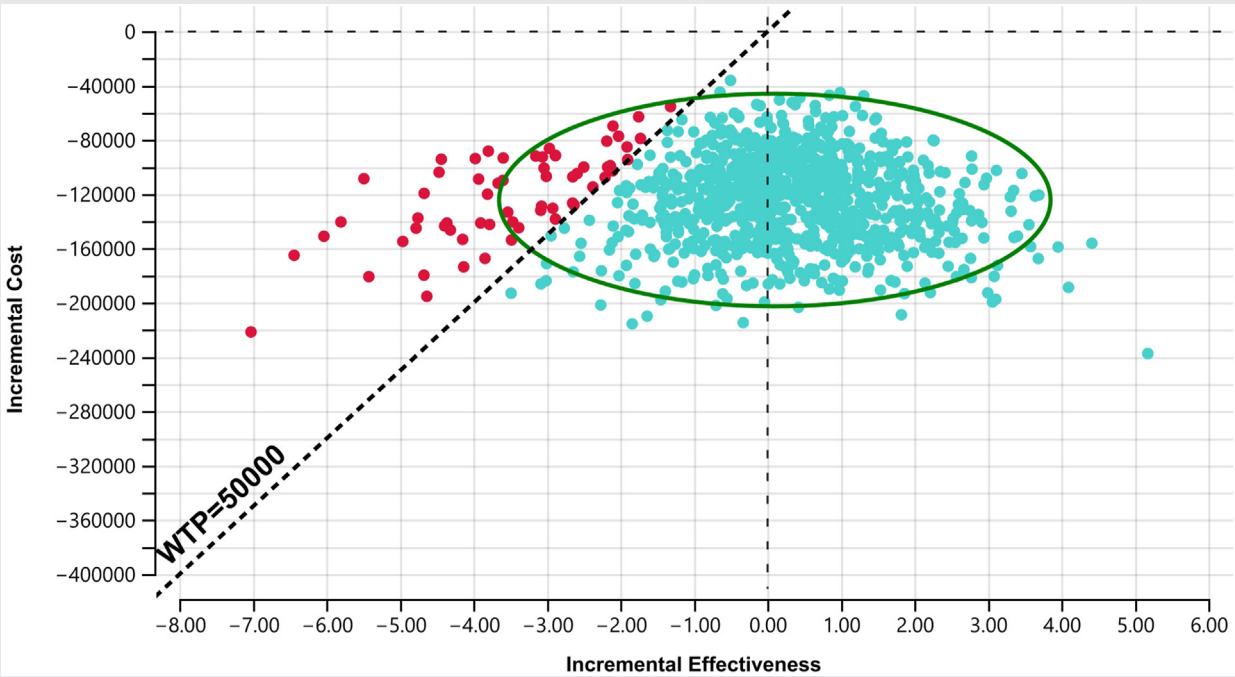
Our model demonstrates that the use of IVF + PGT-M for selection against SCD vs. lifetime SOC treatment for those affected by the disease is the dominant strategy and most cost-effective for the healthcare sector in the United States. Within the base-case analysis, assuming a lifetime SCD SOC treatment cost of $339,270 vs. a lifetime IVF + PGT-M derived nonSCD treatment cost of $201,676, an incremental savings of $137,594 was demonstrated with a gain of 1.96 QALYs and 3.69 life years over a lifetime.

On performing sensitivity analysis within the mild, moderate, and severe disease categories, SOC treatment never met equivalent cost-effectiveness. We found the SOC cost for mild SCD to be the most influential variable, followed by the yearly mortality probability of an individual with SCD. All costs included in SOC for mild SCD resulted in incremental cost-effectiveness ratios (ICERs) below the WTP threshold of $50,000. Any yearly mortality probability for SCD >0.058 produced an ICER below the WTP threshold of $50,000 per QALY. Although not the major factors driving our model results, variation in certain parameters—including the probability of mortality for an individual without SCD (values between 0.03 and 0.18), the yearly utilities for both individuals with (0.98 and greater) and without SCD (between 0.25 and 0.63), and the probability of an individual being born with SCD (0.028 and lower)—resulted in ICERs that were above the WTP threshold. In each case, these are extreme values that would be unlikely to occur in actual clinical practice. For reasonable values of all parameters, IVF + PGT-M was both less costly and more effective than a natural conception in know-carrier parents.

A strength of our study is the use of a conservative WTP threshold of $50,000 per QALY. Probabilistic analysis demonstrated the dominance and cost-effectiveness of IVF + PGT-M across all severities of SCD SOC at this WTP threshold, indicating cost-effectiveness will only improve with an increase in WTP to $100,000 or $150,000 per QALY, as is commonly used in current healthcare cost-effectiveness literature.

An additional strength of our study is the consideration of the need for multiple embryo transfer events to achieve a live birth, with up to three attempts considered within the cost analysis. Pertransfer and cumulative live birth rates were derived from those undergoing single euploid frozen embryo transfer, with a mean age of 35.4 years at first oocyte retrieval. Although the selection of euploid embryos may negate the many negative effects of age on reproductive efficiency, there remains a known negative correlation between maternal age and live birth rates (31). When seeking IVF + PGT-M earlier in one's reproductive life because of known carrier status, a percentage of couples may only require one or two transfers to achieve a live birth, making the use of IVF + PGT-M even more cost-effective

FIGURE 2



Scatterplot on the cost-effectiveness plane of probabilistic sensitivity analysis from 10,000 Monte Carlo simulations.

Combs. Cost effectiveness of PGT for sickle cell. Fertil Steril Rep 2023.

than our model predicts. Although rare, some couples may require more than three euploid embryo transfers, resulting in our model underestimating the actual cost of the IVF + PGT-M treatment arm.

One limitation of the current study is the reliance on extrapolated cost data and transition probabilities between each disease state, as derived from Salcedo et al. (19). Because of a wide variance in SCD severity and treatment across an affected individual's lifetime, the characterization of SOC treatment costs is difficult to objectively define. The inclusion of costs for alternative therapies such as hematopoietic stem cell transplants and gene therapy makes cost data inputs even more obtuse. Our cost parameters were extrapolated from the reported regression results using a weighted average of the parameters for the two genders analyzed separately to get one result. This caused a significant amount of variation, particularly in the standard costs of care for the moderate state of SCD and male patients in general. This variation can be seen in the initial cost of SOC for moderate SCD being lower than the SOC for mild SOC. Reliance on actual cost data for each of these states would eliminate this variation and solely rely on regression results.

Additionally, the cost of yearly SOC for those without SCD was also simplified, resulting in the same nominal amount each year. This would alter with age and other potential comorbidities. The model did not incorporate potential insurance coverage or supplementation into the cost, which is another limitation given the increase in coverage of fertility care and treatment across the United States.

Although our model provides a reasonable approximation of the healthcare costs associated with SCD, it is likely an underestimate is given that indirect costs were not included in our analysis. One such cost is the financial strain placed on an individual's family and caregivers, which may include travel to and from appointments, assistance with medication or treatment costs, and potential missed work. Additionally, depending on the severity of the disease, individuals with SCD may be unable to maintain or keep professional positions, thus placing further pressure on an already costly disease.

CONCLUSIONS

We explored the cost-effectiveness of using preimplantation genetic testing for selection against sickle cell disease versus SOC treatment for those affected by sickle cell disease in the United States using a decision analytic model. Our base-case model suggests IVF + PGT-M is the dominant strategy across all SCD severity categories, with probabilistic sensitivity analysis demonstrating SOC treatment never meets equivalent cost-effectiveness despite a wide variance in cost parameters and WTP thresholds.

When focused on high-risk, dual carrier populations undergoing IVF, the cost of preconception sickle cell screening has been shown to be cost-effective when compared with no screening in mandated states by Harris et al. (32). No current literature exists regarding the cost-effectiveness of screening all prenatal patients for carrier status; however, a

standard hemoglobinopathy panel can be obtained for as little as $45 (33). When adding this cost to our model, IVF + PGT-M remained the dominant strategy in all iterations. When considering that ubiquitous newborn screening has been in place since 2006, preconception screening costs will soon become a moot point as those newborns, now reaching reproductive age, should have carrier status data available. Lack of carrier status knowledge or action on said knowledge represents a communication failure within our healthcare system.

Because of the wide variance in SCD severity and treatment across an affected individual's lifetime, our findings may not be applicable to all afflicted by the disease. The characterization of SOC treatment costs is difficult to estimate on the basis of these variances. Alternative therapies such as hematopoietic stem cell transplants and gene therapy represent extremes that may be only available to those with the most severe disease presentations. Since 2004, the Sickle Cell Treatment Act has provided combined federal and state-derived coverage of 70%–80% of treatment costs, namely dialysis (34). Leveraging this funding into a more cost-effective solution to the disease could provide exponential benefit, especially to those minority groups disproportionally affected and with limited healthcare access.

In vitro fertilization with preimplantation genetic testing for monogenic disease represents an alternative to after-the-fact treatment by selecting against the birth of SCD-affected individuals in the first place. Historically, the use of this testing could have been considered extreme but is now widely available across many parts of the world. Within the United States, states with mandated coverage for treatment reduce the cost of IVF for individuals even further, making use of this technology within reach for more patients. On the basis of our findings, we objectify the anecdotal understanding that preventing SCD is more cost-effective than treatment. More importantly, a cost-effectiveness analysis will never capture the level of individual pain, suffering, and altered expectations that SCD brings to bear. Experimental therapies will always have their place with the future hope of curing those already afflicted, but the ability to prevent SCD is already at hand. Increased awareness of the importance of screening for SCD carrier status and access to IVF + PGT-M for couples found to be carriers is key to reducing the burden SCD places on our healthcare system.

REFERENCES

1. Data and statistics on sickle cell disease. Centers for Disease Control and Prevention; 2022.
2. Pinto VM, Balocco M, Quintino S, Forni GL. Sickle cell disease: a review for the internist. Intern Emerg Med 2019;14:1051–64.
3. American Academy of Pediatrics. sickle cell disease: information for parents. Available at: https://www.healthychildren.org/English/health-issues/conditions/chronic/Pages/Sickle-Cell-Disease-in-Children.aspx.
4. ACOG Committee on ObstetricsACOG Practice Bulletin No. 78. ACOG Practice Bulletin No. 78: hemoglobinopathies in pregnancy. Obstet Gynecol 2007;109:229–37.
5. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet 2010;376:2018–31.
6. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. N Engl J Med 2017;376:1561–73.
7. Meier ER. Treatment options for sickle cell disease. Pediatr Clin North Am 2018;65:427–43.
8. Practice advisory: hemoglobinopathies in pregnancy; August 2022. American College of Obstetricians and Gynecologists. Available at: https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2022/08/hemoglobinopathies-in-pregnancy.
9. Gregg AR, Aarabi M, Klugman S, Leach NT, Bashford MT, Goldwaser T, et al. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med 2021;23:1793–806.
10. De Rycke M, Berckmoes V. Preimplantation genetic testing for monogenic disorders. Genes (Basel) 2020;11:871.
11. Stocker E, Johal S, Rippel L, Darrah R. Frequency of embryos appropriate for transfer following preimplantation genetic testing for monogenic disease. J Assist Reprod Genet 2022;39:2043–50.
12. The use of preimplantation genetic testing for aneuploidy (PGT-A): a committee opinion. Fertil Steril 2018;109(3):429–36.
13. Attia M, Kripalani S, Darbari I, Nickel RS. Parents of children with sickle cell disease are interested in preimplantation genetic testing. J Pediatr 2020;223:178–82.e2.
14. Khorshid A, Boyd ALH, Behr B, Zhao Q, Alvero RJ, Bavan B. Average cost of in vitro fertilization with preimplantation genetic testing for monogenic disorders and aneuploidy per unaffected live birth for carrier couples. Fertil Steril 2021;116:e374–5.
15. Neal SA, Morin SJ, Franasiak JM, Goodman LR, Juneau CR, Forman EJ, et al. Preimplantation genetic testing for aneuploidy is cost-effective, shortens treatment time, and reduces the risk of failed embryo transfer and clinical miscarriage. Fertil Steril 2018;110:896–904.
16. Crawford S, Boulet SL, Mneimneh AS, Perkins KM, Jamieson DJ, Zhang Y, et al. Costs of achieving live birth from assisted reproductive technology: a comparison of sequential single and double embryo transfer approaches. Fertil Steril 2016;105:444–50.
17. Lipton JH, Zargar M, Warner E, Greenblatt EE, Lee E, Chan KKW, et al. Cost effectiveness of in vitro fertilisation and preimplantation genetic testing to prevent transmission of BRCA1/2 mutations. Hum Reprod 2020;35:434–45.
18. Wonder CDC. CDC wonder mortality data.
19. Salcedo J, Bulovic J, Young CM. Cost-effectiveness of a hypothetical cell or gene therapy cure for sickle cell disease. Sci Rep 2021;11:10838.
20. Paulukonis ST, Eckman JR, Snyder AB, Hagar W, Feuchtbaum LB, Zhou M, et al. Defining sickle cell disease mortality using a population-based surveillance system, 2004 through 2008. Public Health Rep 2016;131:367–75.
21. Jung J. Estimating markov transition probabilities between health States in the HRS dataset; 2006.
22. Alemayehu B, Warner KE. The lifetime distribution of health care costs. Health Serv Res 2004;39:627–42.
23. Pirtea P, De Ziegler D, Tao X, Sun L, Zhan Y, Ayoubi JM, et al. Rate of true recurrent implantation failure is low: results of three successive frozen euploid single embryo transfers. Fertil Steril 2021;115:45–53.
24. Katz P, Showstack J, Smith JF, Nachtigall RD, Millstein SG, Wing H, et al. Costs of infertility treatment: results from an 18-month prospective cohort study. Fertil Steril 2011;95:915–21.
25. Wu AK, Odisho AY, Washington SL 3rd, Katz PP, Smith JF. Out-of-pocket fertility patient expense: data from a multicenter prospective infertility cohort. J Urol 2014;191:427–32.
26. Bakkensen JB, Flannagan KSJ, Mumford SL, Hutchinson AP, Cheung EO, Moreno PI, et al. A SART data cost-effectiveness analysis of planned oocyte cryopreservation versus in vitro fertilization with preimplantation genetic testing for aneuploidy considering ideal family size. Fertil Steril 2022;118:875–84.
27. Khorshid A, Boyd ALH, Behr B, Zhao Q, Alvero R, Bavan B. Cost-effectiveness of IVF with PGT-M/A to prevent transmission of spinal muscular atrophy in offspring of carrier couples. J Assist Reprod Genet 2023;40:793–801.
28. Facadio Antero M, Singh B, Pradhan A, Gornet M, Kearns WG, Baker V, et al. Cost-effectiveness of preimplantation genetic testing for aneuploidy for fresh donor oocyte cycles. F S Rep 2021;2:36–42.

29. Jiang R, Janssen MFB, Pickard AS. US population norms for the EQ-5D-5L and comparison of norms from face-to-face and online samples. Qual Life Res 2021;30:803–16.
30. Lubeck D, Agodoa I, Bhakta N, Danese M, Pappu K, Howard R, et al. Estimated life expectancy and income of patients with sickle cell disease compared with those without sickle cell disease. JAMA Netw Open 2019; 2:e1915374.
31. Reig A, Franasiak J, Scott RT Jr, Seli E. The impact of age beyond ploidy: outcome data from 8175 euploid single embryo transfers. J Assist Reprod Genet 2020;37:595–602.
32. Harris BS, Peipert BJ, Havrilesky LJ, Acharya KS. Cost Effectiveness Analysis of Universal Screening for Sickle-Cell Trait prior to IVF in States with and without an IVF Insurance Mandate. Fertility and Sterility American Society of Reproductive Medicine conference. Virtual Meeting 2020;114(3): e410–1.
33. Labaccess Partnership (LAP) Program. Available at: http://www.losolivos-obgyn.com/info/general_health/labcorp%20cash%20prices.pdf.
34. Catalyst C. The Sickle Cell Treatment Act of 2003: The Law's Provisions and Opportunities for Advocacy Policy Brief. Available at: https://www.communitycatalyst.org/doc-store/publications/SCTA-Paper-FINAL-1.pdf#:~:text=The%20Sickle%20Cell%20Treatment%20Act%20%28SCTA%29%20provides%20an,will%20improve%20health%20outcomes%20for%20individuals%20with%20SCD.