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Projected clinical and economic benefits of improved patent foramen ovale testing among cryptogenic stroke patients in the United States

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ABSTRACT

Background: Accurate determination of stroke etiology is essential for effective secondary stroke prevention, yet 25% to 40% of ischemic strokes are classified as cryptogenic. Patent foramen ovale (PFO), a common finding in cryptogenic stroke, elevates the risk of strokes. However, underuse of diagnostic practices may lead to underdiagnosis of PFO, missing opportunities for guideline-recommended PFO closures and preventable recurrent strokes. This study estimates the value of improving testing for PFO among patients with cryptogenic stroke in the US.

Methods: A cost-effectiveness analysis was conducted, employing a hybrid model including a decision tree and a Markov model to assess health outcomes and economic impacts from a US payor perspective over a life-time horizon. The model compared two PFO testing scenarios: the Current Diagnostic Scenario (54% testing) and Optimal PFO Diagnostics (100% testing). The decision tree evaluated diagnostic pathways for PFO (TTE, TEE, TCD), while the Markov model simulated patient progression through various health states (recurrent ischemic stroke, TIA, and death). Cost-effectiveness was determined using the incremental cost-effectiveness ratio (ICER) with a willingness-to-pay threshold of $75,000 per Quality-Adjusted Life Year (QALY).

Results: In a simulated cohort of 1,000 patients, increasing the diagnostic testing rate for PFO from 54% to 100% is expected to prevent 63 recurrent strokes, resulting in 23 life years saved and 286 QALYs gained. This led to cost-savings of $1.9 million for payors, indicating a dominant economic position (ICER = -$6,770/QALY). The model estimated screening four patients would lead to identifying and closing one PFO, while screening seven would prevent one recurrent stroke. Thorough sensitivity analyses confirmed the robustness of these findings.

Conclusions: Improving PFO diagnostic testing among patients with cryptogenic stroke is projected to result in improved health outcomes for patients, while yielding cost-savings, underscoring the importance of adhering to PFO diagnostic guidelines.

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Introduction

Patent foramen ovale (PFO) is an opening between the heart's atria that usually closes after birth but remains open in about 25% of the general population[1]. This can allow emboli to bypass the lungs and enter systemic circulation, increasing the risk of ischemic stroke[2,3]. Approximately 795,000 strokes occur annually in the United States (US), with ischemic strokes accounting for 87% of cases. Of these, 77% are non-lacunar, involving larger artery blockages. Nearly 45% of non-lacunar strokes are cryptogenic, with

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no identified cause—some of which may be PFO-associated[4]. As a result, PFO is a potential cause in roughly 240,000 cryptogenic stroke patients annually, underscoring the potential value of its diagnosis and treatment in improving stroke care.

Identifying PFO as the cause of stroke and excluding other potential etiologies is essential for providing optimal care for patients and preventing recurrent strokes[5], and reducing the estimated $1.3 billion annual financial burden of PFO-associated strokes in the US[6]. Several diagnostic algorithms have been developed to identify stroke etiology[4,7,8], and an estimated 50% of patients initially classified with cryptogenic stroke may actually have a PFO-related stroke caused by paradoxical embolism[9]. The PFO-attributable fraction—the likelihood that a cryptogenic stroke is due to a PFO—increases with factors such as younger age and absence of traditional vascular risk factors[10].

First line PFO testing can be done using transthoracic echocardiography (TTE), either with or without bubble, or Transcranial Doppler (TCD) and approaches vary across practices in the United States (US). TTE is a non-invasive method and has high specificity, making it a useful first-line diagnostic tool for detecting a PFO[11]. TCD continuously monitors cerebral blood flow, offering greater sensitivity but lower specificity compared to TTE[11]. If these tests indicate the presence of a PFO, a transesophageal echocardiography (TEE) with a bubble study can be done for confirmation[11]. TEE is the gold standard and is highly sensitive and specific but is more invasive.

After the initial diagnosis of cryptogenic stroke by a neurologist, cardiologists are typically responsible for diagnosing PFO and evaluating other cardiovascular causes of embolic stroke before recommending PFO closure[4,7,8]. PFO closure refers to the sealing of a PFO, typically performed using a transcatheter closure device or, rarely, through open-heart surgery. In this study, we focus on percutaneous device closure, as supported by multiple clinical trials and guidelines. For individuals aged 18–60 who experienced a PFO-associated stroke, international guidelines recommend PFO closure combined with medical therapy as the preferred treatment over medical therapy alone[4,7,8]. This recommendation is supported by substantial evidence demonstrating that PFO closure significantly reduces the risk of recurrent strokes. Prior studies demonstrate that PFO closure decreases the odds of ischemic stroke (OR 0.22, 95% CI 0.13–0.36) and transient ischemic attack (TIA) (OR 0.57, 95% CI 0.34–0.98) compared to medical therapy alone[12], while providing superior cost-effectiveness[13,14].

Despite clear evidence supporting the importance of accurate diagnostics to ensure optimal care for cryptogenic stroke patients, PFO diagnostic testing is performed in only 54% of eligible cases[15]. This underuse may be explained in part by limited access to specialized testing, patient aversion to invasive testing procedures, or clinical or financial uncertainty about the benefit of increased testing in certain patient populations. As a result, opportunities to reduce the risk of future strokes may be missed, as patients with undiagnosed PFO-associated stroke might not receive the most effective secondary stroke prevention[12]. This study aimed to evaluate the cost-effectiveness of improving PFO diagnostic testing among patients with cryptogenic stroke in the US.

Methods

A cost-effectiveness analysis (CEA) was conducted to estimate the health and economic outcomes from improving adherence to guideline-driven diagnostic testing of PFO among patients with a history of cryptogenic stroke. This economic analysis was from the perspective of payors in the US healthcare system. This perspective aligns with the intended use of the model in informing reimbursement decisions by US healthcare payors and decision makers.

Intervention and comparator

We compared the cost-effectiveness of two diagnostic scenarios: the Current Diagnostic Scenario (comparator), in which an estimated 54% of patients undergo diagnostic evaluation for PFO[15], and the Optimal PFO Diagnostics Scenario (intervention), in which 100% of patients are evaluated for PFO, simulating full implementation of guideline-recommended diagnostic practices.[4]

Study design

We developed a hybrid economic model, combining a decision tree with a Markov model to reflect the patient pathway and capture health and economic outcomes associated with diagnosing and managing PFOs to prevent recurrent strokes. A 3% annual discount rate was employed for both health and economic outcomes, aligning with the guidelines of the Institute for Clinical and Economic Review's 2023 Value Assessment Framework.[16] A life-time horizon was applied in the base case to capture all relevant health outcomes and costs, while five- and ten-year horizons were evaluated in scenario analyses. To assess the cost-effectiveness of Optimal PFO Diagnostics, a willingness to pay (WTP) threshold of $75,000 per QALY was applied, which adheres to the recommended WTP range between $50,000 and $150,000 per QALY in the US[16].

This model was built in alignment with the value assessment framework of the Institute for Clinical and Economic Review[16]. The study design and reporting of the CEA adhered to the diagnostic-specific guidance for cost-effectiveness analyses outlined by van der Pol et al. who have adapted the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) criteria to diagnostics (Table S1)[17].

Model structure

A hybrid modeling structure was employed, combining a decision tree and a Markov model. The decision tree—a widely employed technique in health economic analyses, particularly for screening and diagnostics[17] was used to represent the sequence of events associated with the initial diagnostic process, leveraging its unidirectional flow to provide a rigorous, intuitive, and transparent framework for modeling short-term costs and outcomes. To accurately reflect long-term disease progression, including recurrent events and transitions between health states, a Markov model was integrated to capture ongoing follow-up and treatment pathways over time[18].

As shown in Figure 1, the initial phase of the model, covering the patient journey from diagnosis to appropriate stroke management, was represented by a decision tree. The subsequent phase of the model analyzed the health and economic outcomes of treating and managing patients, based on the outcomes of the decision tree, using a Markov health-state transition model, as illustrated in Figure 2. The decision-tree design was derived from publicly available diagnostic algorithms[4,7,8] and was validated with input from clinical experts. The Markov model was developed based on previously published models on PFO closure and validated by clinical experts[13,19–21]. Model development adhered to standard modeling practices[18]. To ensure model face validity, two leading physicians and PFO-associated stroke experts assessed the appropriateness and validity of the model assumptions and structure. The physicians provided guidance to ensure the model best matched the patient journey, and provided input on health state definition, time horizon, age-based definitions and epidemiological input into the model. Based on their feedback, modifications were made to enhance the model's clinical relevance and accuracy.

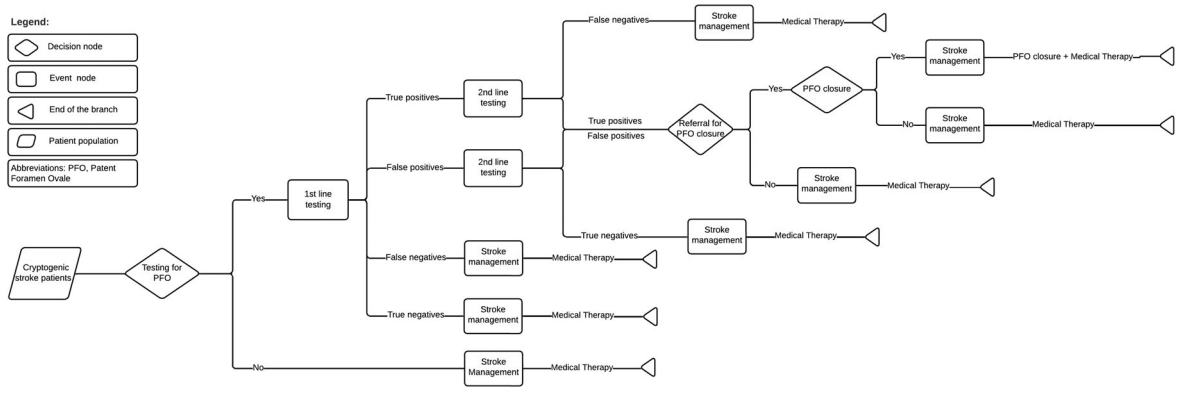

Figure 1. Model structure of the decision tree simulating diagnostic work-up of PFO in cryptogenic stroke patients.

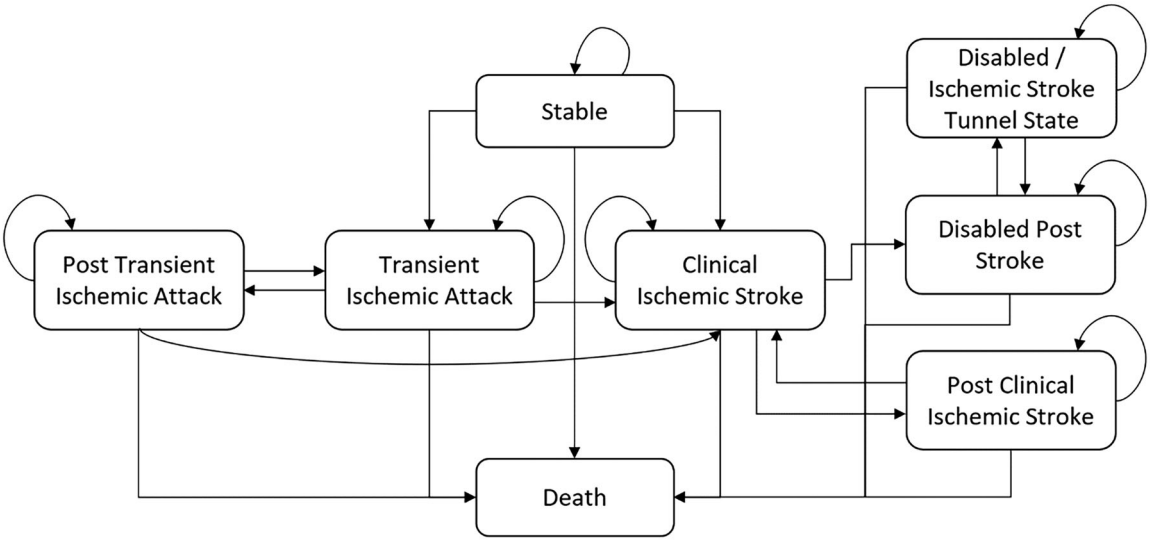

Figure 2. Model structure of the Markov model simulating the post-diagnostic follow-up and management of patients after cryptogenic stroke. Health states are represented by boxes, while arrows indicate transitions.

The decision-tree model estimated the number of patients with a PFO-associated stroke who would benefit from either PFO closure or, alternatively, medical therapy alone. These estimates were used to determine the number of patients receiving each treatment in the Markov model and to calculate corresponding treatment-related costs and health outcomes under each scenario. The health states and patient pathways within the Markov model were consistent across both treatment arms—medical therapy alone and PFO closure. However, transition probabilities and health utilities varied depending on the treatment received.

Decision tree for the diagnostic workflow of patients

The decision tree featured six branches (pathways), each leading to patients receiving either medical therapy alone or a combination of PFO closure alongside medical therapy. The decision tree served as an input to feed patients into the Markov model, which simulated their post-treatment follow-up. The branches were delineated by pivotal decisions and events, as illustrated in Figure 1. Based on the diagnostic testing rate for PFO, the first decision node determined the percentage of patients who underwent first-line testing with a TTE in the base case model (alternatively, TCD was considered in a scenario analysis)[11,22]. The patients who did not undergo PFO testing were classified as having an embolic stroke of undetermined source (ESUS) and received medical therapy. Based on PFO incidence and the sensitivity and specificity of TTE, patients with a positive TTE underwent second-line testing with TEE to confirm the presence of PFO[11,22,23], while those testing negative received medical therapy. When second-line testing confirmed the presence of a PFO, patients deemed eligible by the physician were assumed to undergo successful PFO closure surgery. Patients that were ineligible, or declined surgery, were assumed to receive medical therapy, like those testing negative during second-line testing. In the base case, the model assumed that all patients were eligible for and accepted the closure procedure.

Markov model for post-diagnostic follow-up and management of patients

The Markov model is a commonly used method for decision analysis in measuring the value of diagnostic technologies[24]. This model consisted of eight health states that represented the experience of cryptogenic stroke patients over time. After experiencing a stroke, the diagnostic workup, and receiving treatment, all patients began in the "stable" health state. From there, patients either remained stable or experienced one of three events (1) recurrent ischemic stroke, (2) transient ischemic attack (TIA), or (3) death. After a recurrent stroke or TIA, patients would then transition to the corresponding post-event health state. Depending on whether patients were treated with medical therapy alone or PFO-closure combined with medical therapy, the risk of recurrent stroke and recurrent TIA differed.

Patients in the TIA, post-TIA, recurrent stroke, and post-stroke health states could not move back to the stable state. The disabled post-stroke state had a tunnel state—Disabled + recurrent stroke—after which patients either returned to the disabled post-stroke state or moved to the death state. Patients in the disabled post-stroke state could not move back to states other than the tunnel or death state. The death health state was absorbent—once in this state, patients could not move to other health states.

The distinction between the post clinical ischemic stroke state and the disabled post-stroke state lies in stroke severity and resulting disability. Patients who experience a severe stroke leading to institutionalization transition to the disabled post-stroke state[25]. We assumed that once a patient enters the disabled state, recovery to a non-disabled state is not possible. However, these patients remain at risk for recurrent strokes. To avoid incorrectly transitioning them back to the clinical ischemic stroke state—and thus out of the disabled post-stroke state—we introduced a tunnel state: the disabled/ischemic stroke tunnel. This structure ensures accurate representation of disease progression for patients with long-term disability.

Cost and utility data were applied to patients in each health state. In line with previous models, a three-month cycle length was deemed the most appropriate to reflect the outcomes of interest after PFO closure[13,19–21]. Background mortality was incorporated into all health states within the Markov model to account for deaths unrelated to PFO-associated strokes, ensuring that the model reflects overall mortality rates in the population. The model assumed no difference in mortality between medical therapy and PFO-closure.

Patient population

As PFO is partly a diagnosis by exclusion, the model assumed patients underwent a typical diagnostic workup according to clinical guidelines for cryptogenic stroke[4,7,8] to rule out other etiologies prior to entering the model. Consequently, this model simulated the experience of a hypothetical cohort of 1,000 cryptogenic stroke patients that either 1) have underlying PFO, or 2) do not have a PFO and would be classified as an ESUS. The average starting age was based on the GORE REDUCE trial (45 years)[26].

Data inputs

In the model, data from the GORE REDUCE trial,[26] evaluating the GORE® CARDIOFORM SEPTAL OCCLUDER, was selected as the representative for all PFO closure devices as its odds of preventing recurrent stroke (OR: 0.24; CI: [0.09, 0.66]) most closely matched the average odds from all PFO closure devices (OR: 0.22; CI: [0.13, 0.83])[12]. This enabled the utilization of recurrent stroke and TIA rates from previous economic models, as well as cost and utility inputs in current research[19].

Diagnostic inputs and transition probabilities

The transition probabilities of the decision tree and Markov model were obtained from the literature and are described in Table 1. The specific transition probabilities of the Markov model for each health state are further described in Supplementary Material 2. In the literature, the specificity and sensitivity of the TCD and TTE tools were reported relative to the outcomes of TEE. As the absolute values were required, these were calculated based on the absolute sensitivity and specificity for TEE[30], TTE[28], and TCD[28]. Full calculations are provided in Supplementary Material 3.

Cost data

This model was designed to comprehensively capture relevant costs for the payor in the US related to the diagnosis of PFO and the post-stroke management of patients to ensure the health economic model's accuracy. Unit costs were sourced from publicly accessible US fee schedules published by the Center for Medicare & Medicaid Services (CMS), supplemented with published literature for long-term costs[19,33–37]. All costs were reported in 2023 USD, using the Consumer Price Index for medical care to adjust for inflation[38]. The base case model only considered direct costs, while indirect costs (such as productivity losses) were included in a scenario analysis featuring a societal perspective. The breakdown

Table 1. Model parameters and values.

Model parameter	Values
Decision-tree inputs	
Incidence PFO in CS patients	41.24%[27]
Current diagnostic scenario	54.00%[15]
Optimal PFO diagnostics	100% (assumption)
TCD specificity*	81.81%[28]
TCD sensitivity*	84.70%[28]
TTE specificity*	91.55%[29]
TTE sensitivity*	65.90%[29]
TEE specificity	91.40% (95% CI: 82.3–96.8%)[30]
TEE sensitivity	89.20% (95% CI: 81.1–94.7%)[30]
PFO referral rate	100% (assumption)
PFO acceptability rate	100% (assumption)
Markov model inputs	
Risk of TIA (PFO closure)	0.07%[19]
Risk of TIA (MM)	0.18%[19]
Risk of ischemic stroke (PFO closure)	0.11%[19]
Risk of ischemic stroke (MM)	0.43%[19]
Post-clinical ischemic stroke to clinical ischemic stroke	1.14%[31]
Risk of disability after stroke	2.30%[25]
Mortality from stable states (PFO closure)**	0.00%[26,32]
Mortality from stable states (MT)	0.00%[26]
Post-stroke mortality	0.14%[31]

*Calculated values.
**Mortality data from the REDUCE and RESPECT trials indicated that the reported deaths were not connected to the device, procedure, or treatment. Based on this finding, the model excluded any added risk of mortality after surgery to avoid artificially increasing mortality rates.
Abbreviations: PFO, patent foramen ovale; CS, cryptogenic stroke; TCD, Transcranial Doppler; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; TIA, transient ischemic stroke; MM, medical therapy.

Table 2. Direct costs breakdown.

Cost specification	Costs per unit	Units per year	Units per cycle	Costs per cycle
Decision tree				
TCD	$169[39]	–	–	–
TTE	$339[39]	–	–	–
TEE	$702[39]	–	–	–
Markov model				
Diagnostics	$2,747[33,39]	-	1	$2,747
TIA treatment event costs	$7,607[19]	-	1	$7,607
Hospitalization ischemic stroke	$29,009[34]	-	1	$29,009
Long-term care costs stroke (annual)	$6,411[36]	1	0.25	$1,602
Institutionalization (annual)	$105,889[35]	0.732	0.183	$19,377
GP visit	$57[39]	1	0.25	$14
Device placement costs*	$16,707[37]	-	1	$16,707
Antithrombotic medication**	$458[19]	-	1	$458
• Aspirin	$4.21			
• Clopidogrel	$12.41			
• Dipyridamole with Aspirin	$441.76			

*Device placement costs were assumed to be outpatient costs, which was validated by clinical experts.
**Costs for antithrombotic medication were weighted by usage according to Saver et al. 2017[32].
Abbreviations: TCD, Transcranial doppler; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; TIA, transient ischemic attack; GP, General practitioner.

of direct costs is shown in Table 2. Supplementary Material 4 offers a detailed breakdown of both direct and indirect costs, along with costs per health state.

Utility data

Utilities were used to calculate the quality-adjusted life years (QALYs) of the two cohorts over the time horizon of the model. Utilities for each health state were obtained from the publicly accessible literature. An overview of the utilities for each health state is provided in Supplementary Material 5.

This model assumed that undergoing the actual cardiac workup for PFO evaluation and other standard diagnostic processes do not directly impact health utility/quality of life. Utility values for the health states in the Markov model were sourced from Volpi et al.[19] when possible, which used a similar Markov structure. Patients who were disabled after a stroke were assigned a new baseline utility value of 0.406, based on Luengo-Fernandez et al. (2013)[40]. Lastly, in the societal perspective scenario, the model

assigned a caregiver disutility of 0.112 to 36.8% of patients in the stroke, TIA, and disabled post-stroke health state[41–43]. The calculation of caregiver disutility is provided in Supplementary Material 6.

Adverse events

Costs of serious adverse events (SAEs) related to the PFO closure device or procedure were calculated (Supplemental Material 7) and included in the model. SAEs related to medical therapy were excluded due to the fact that PFO closure patients were assumed to continue medical therapy after closure[14].

Model outcomes

The health and economic outcomes of Optimal PFO Diagnostics were compared to the outcomes of the Current Diagnostic Scenario. Each scenario's total costs, health outcomes, incremental cost-effectiveness ratio (ICER), and net monetary benefit (NMB) were estimated. Health outcomes included QALYs, Life Years (LYs), and prevented strokes. Additionally, calculations were performed to determine the number of patients that must be screened to successfully close a single PFO and to prevent one recurrent stroke.

The ICER quantifies the additional cost required to gain one QALY or LY by switching from the Current Diagnostic Scenario to Optimal PFO Diagnostics. It is calculated by dividing the difference in total costs by the difference in QALYs between the two scenarios, providing a standardized measure of cost-effectiveness. A lower ICER indicates better cost-effectiveness, as it reflects a lower cost per additional health benefit. The Optimal PFO Diagnostics scenario is considered cost-effective if its ICER falls below the pre-set threshold—indicating the additional health benefit per dollar spent is desirable. When the ICER is negative, it is preferable to use the NMB to assess cost-effectiveness. This avoids ambiguity, as a negative ICER can result from either a dominant strategy (more effective and less costly) or a dominated one (less effective and more costly), making interpretation less straightforward[44].

Alternatively, the NMB evaluates cost-effectiveness by comparing the cost of Optimal PFO Diagnostics to the benefits it provides, based on a pre-set willingness-to-pay (WTP) threshold. The NMB is calculated as the monetary difference between the WTP value and the ICER, using the following equation:

$$NMB = (\Delta QALY \times WTP) - \Delta Costs$$

A positive NMB value indicates cost-effectiveness, and a higher NMB reflects greater cost-effectiveness, as it shows that health benefits outweigh costs at the given WTP threshold.

Scenario and sensitivity analyses

In the base case model, 54 input parameters were varied one at a time in the deterministic sensitivity analysis (DSA) to assess the effects of individual parameter uncertainty on the model outcomes. Further, a probabilistic sensitivity analysis (PSA) was conducted, in which all 54 parameters were varied simultaneously in every iteration of the analysis. Each iteration involved sampling the input parameters from their respective probability distributions, reflecting the uncertainty associated with each parameter. By running multiple simulations with different sets of parameter values, the PSA provided insights into the range of possible outcomes and their probabilities, capturing the overall robustness of the model. A total of 1,000 iterations were run to ensure an accurate PSA result. For the DSA and PSA, confidence intervals for input parameters were utilized whenever available. In cases where confidence intervals were not available, a range estimate of ±20% was applied to all parameters, except for utility values, where a range estimate of ±5% was applied (to avoid unrealistic/illogical combinations of health utilities).

To test and validate the impact of key assumptions and modeling decisions that were made, 21 scenarios were analyzed to test the robustness of the findings. This included analyzing the acceptance and referral rates for PFO closure, changes in the diagnostic workup, and the proportion of stroke patients currently tested for PFO. While traditional sensitivity analyses typically evaluate the influence of varied input parameters on the ICER, we have opted to use NMB in our model's sensitivity analysis. This decision is prompted by encountering negative ICER values in a number of tested scenarios, which makes the interpretation of the results less intuitive[44].

Results

Base case results

This model reported that Optimal PFO Diagnostics (100% tested) performed the best and was expected to prevent 63 recurrent strokes compared to the Current Diagnostic Scenario (54% tested), resulting in 23 life years saved and 286 QALYs gained in a simulated cohort of 1,000 patients over a life-time horizon, as presented in Table 3. Optimal PFO Diagnostics led to a total expected cost savings of $1.9 million per 1,000 patients, resulting in being Dominant, an economic term meaning it improved health outcomes and achieved lower costs [ICER of -$6,770 (savings) per QALY gained, with an NMB of $23.4 million]. The health benefits and costs saved in the base case outcomes of this model indicated that Optimal PFO Diagnostics is cost-saving and dominant over the Current Diagnostic Scenario for PFO. The analysis revealed that approximately four patients were required to be screened to identify and close one PFO, while seven screenings were required to prevent a single recurrent stroke. A more detailed presentation of the deterministic results including disaggregated costs and health gains can be found in Supplementary Material 8.

Deterministic sensitivity analysis (DSA)

In the DSA, illustrated in Figure 3, the NMB ranged from $13,201,192 to $30,290,021, while the NMB of the base case was $23,355,954. The three most influential parameters on the model outcomes were utility (health outcome) for the stable state (PFO closure); the Current Diagnostic Scenario rate; and the Optimal PFO Diagnostics rate. An overview of the DSA results is provided in Supplementary Material 8.

Probabilistic sensitivity analysis

Figure 4 shows the cost-effectiveness plane of Optimal PFO Diagnostics versus the Current Diagnostic Scenario. The cost-effectiveness plane plotted all simulations of the PSA, each containing a unique set of input values, on a graph showing the resulting incremental QALYs gained, and costs incurred. The yellow line signifies the WTP threshold ($75,000/QALY)—all simulations below this line are considered cost-effective.

The PSA reported that Optimal PFO Diagnostics was cost-effective in all 1,000 simulations compared to the Current Diagnostic Scenario, with an average ICER of -$6,708 (Dominant). This can be seen in Figure 4, where all the data points are below the WTP threshold line. Almost all of the iterations are plotted in the east-south quadrant, indicating that Optimal PFO Diagnostics led to both cost savings and improved health outcomes. All iterations were considered cost-effective at a WTP greater than or equal to $5,016.

Scenario analysis

The results of the explored scenarios that were expected to have an impact on the NMB for the Optimal PFO Diagnostics versus the Current Diagnostic Scenario are shown in Figure 5. Comparing these results with the base case NMB of $23.4 million, some scenarios had a considerable impact on the NMB. Two scenarios were conducted in which the diagnostic tools used were altered. In the first scenario, TTE was

Table 3. Base case results of optimal PFO diagnostics versus the current diagnostic Scenario.

Incremental cost-effectiveness ratio			
Specification	Current diagnostic scenario (54% tested)	Optimal PFO diagnostics (100% tested)	Δ Optimal vs. current
Costs	$51,219,680	$49,286,081	−$1,933,599
QALYs	15,600	15,886	286
ICER (cost/QALY)	–	–	*Dominant (−$6,770)
ICER (cost/LY)	–	–	*Dominant (−$83,321)
NMB	–	–	$23,355,954
Clinical outcomes			
Specification	Current diagnostic scenario	Optimal PFO diagnostics	Δ Optimal vs. current
Recurrent strokes	744	681	63
Life years	20,686	20,709	23

Abbreviations: QALY, Quality-adjusted life years; ICER, incremental cost-effectiveness ratio; LY, life years; NMB, net monetary benefit, PFO, patent foramen ovale.
*Dominant indicates the scenario led to both lower costs and improved patient outcomes (QALYs).

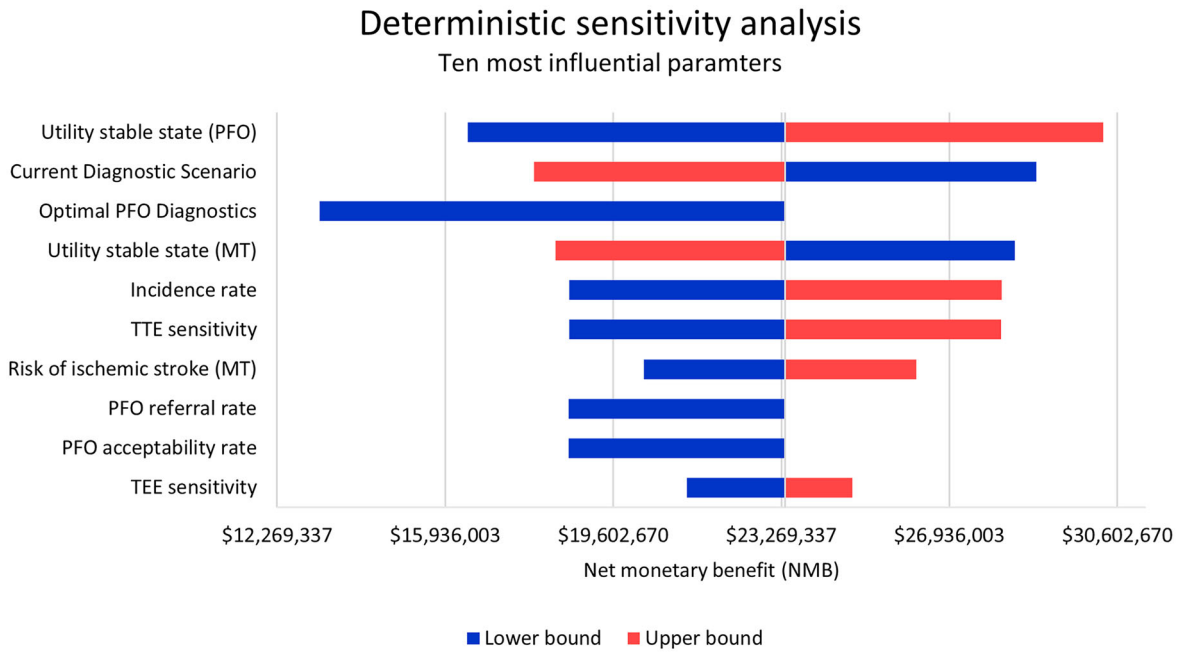

Figure 3. Tornado diagram deterministic sensitivity analysis. Abbreviations: PFO, patent foramen ovale; MT, medical therapy; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography.

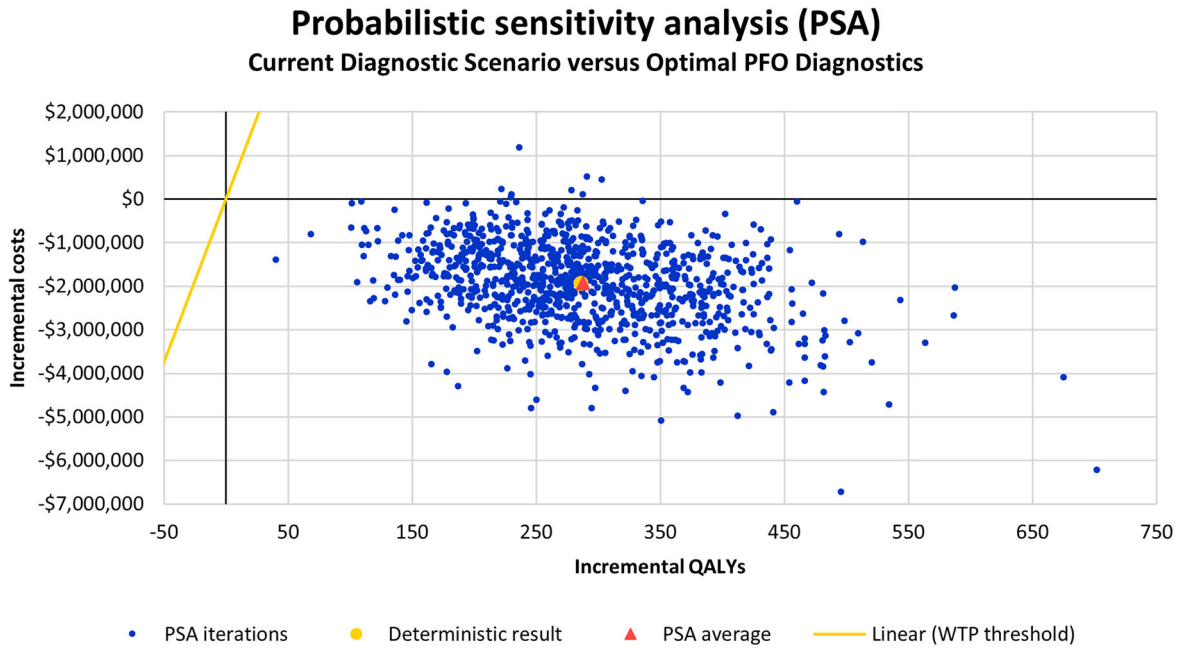

Figure 4. Cost-effectiveness plane probabilistic sensitivity analysis comparing the Current Diagnostic Scenario with Optimal PFO Diagnostics. Abbreviations: QALYs, quality-adjusted life years; WTP, willingness to pay.

substituted with TCD, resulting in an NMB of $30.1 million, while in the second scenario, only TEE was used, yielding an NMB of $35.8 million, indicating that both scenarios are cost-effective. After PFO was confirmed in second-line testing, the referral and acceptance rates for PFO closure significantly impacted the model as lowering these values excluded the benefits of closure while including the costs of testing. Based on a survey of clinicians, two scenarios were conducted, setting the acceptance rate at 59% and the referral rate at 61%, which resulted in a NMB of $13.7 million and $14.1 million, respectively[45]. The utility values assigned to the stable health states of patients undergoing PFO closure and those receiving medical therapy emerged as the first and fourth most impactful parameters, respectively. Reducing both utility values by 25% to 0.6 resulted in an NMB of $4.3 million. Additionally, two scenarios were conducted with the

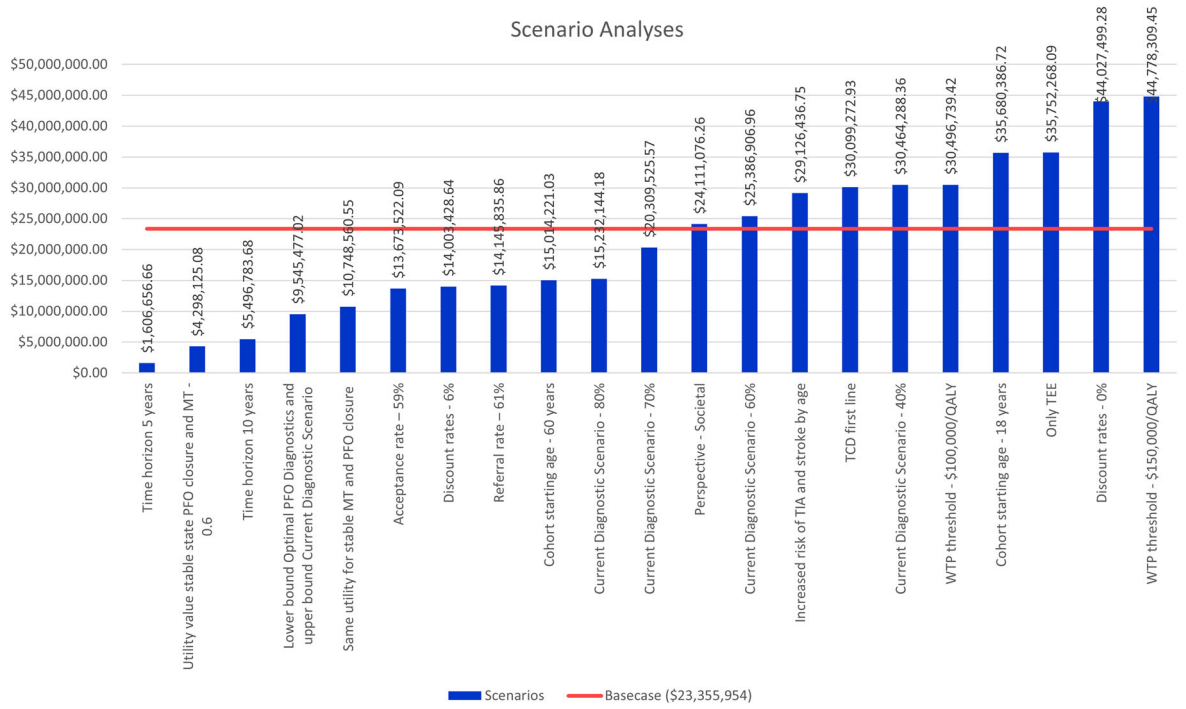

Figure 5. Two-part diverging bar chart scenario analyses (difference from base case).

cohort starting ages 18 and 60 years, which led to implied life-time horizons of 82 and 40 years, respectively. Both scenarios had a positive NMB and are therefore considered cost-effective. Since the current and increased diagnostic testing rates for PFO ranked second and third in terms of influence on model outcomes, and given the uncertainty around the Current Diagnostic Scenario, a scenario using the lower bound of Optimal PFO Diagnostics and the upper bound of the Current Diagnostic Scenario was explored. This scenario resulted in an NMB of $9.5 million. Another scenario was analyzed in which the diagnostic testing rate of the Current Diagnostic Scenario was set to 80%, resulting in an NMB of $15.2 million. Two scenarios were included with a time horizon of 5 and 10 years, resulting in an NMB of $1.6 million and $5.5 million, respectively.

Discussion

This CEA measured the projected value of Optimal PFO Diagnostics in preventing recurrent clinical ischemic strokes among US patients with a history of cryptogenic stroke. Based on this health economic model, employing Optimal PFO Diagnostics was expected to result in 286 QALYs gained while saving payors $1.9 million over a life-time horizon in a simulated cohort of 1,000 patients. Additionally, the increased diagnostic testing rate resulted in an expected gain of 23 additional life years while preventing an expected 63 strokes. Given the substantial health and economic benefits associated with Optimal PFO Diagnostics, it is deemed cost-saving and the best strategy (Dominant) compared to the Current Diagnostic Scenario.

Understanding why the current PFO testing rate is 54% is helpful for evaluating the potential value of an Optimal PFO Diagnostics scenario with full (100%) testing uptake. The underuse of PFO testing may be explained in part by limited access to specialized testing, patient aversion to invasive testing procedures, or clinical or financial uncertainty about the benefit of increased testing in certain patient populations. This cost-effectiveness analysis provides valuable insights into the economic and clinical impact of increasing testing rates. Scenario and sensitivity analyses further support the estimation of its potential value.

The DSA and PSA demonstrated the robustness of the model as well as the cost-utility outcomes, showing that Optimal PFO Diagnostics for cryptogenic stroke patients saved costs for all variations in sensitivity and scenario analyses. To further demonstrate the potential of Optimal PFO Diagnostics, we assumed the referral and acceptance rates at 100% if PFO was confirmed in second-line testing. Because real-world referral and acceptance rates may not reach 100%, the model also included scenarios using

more conservative estimates of 59% and 61%, respectively. Despite the decreased rates, the NMB remained positive in both scenarios. Given that the current diagnostic rates among all providers are yet to be measured, the model employed several additional scenarios applying different diagnostic rates. When the Current Diagnostic Scenario rate was set to 80% (versus 54% in the base case), the Optimal PFO Diagnostics remained cost-effective, with an NMB of $15.2 million. Conservatively, the base-case model did not consider an increased risk of TIA or stroke by age. Including an increased risk of TIA or stroke by age resulted in an increased NMB of $29.1 million. This further demonstrated the value of Optimal PFO Diagnostics, even in less ideal scenarios. Additionally, it highlights the cost-saving opportunities that could follow from additional educational programs aimed at raising awareness about the importance of identifying PFOs and reducing provider, clinician, and patient hesitancy towards PFO testing and closure. These insights verify the importance of continually reassessing and refining diagnostic pathways based on evolving evidence and clinical considerations to ensure optimal patient outcomes, recurrent stroke prevention and resource utilization.

There are limitations in this study that have been identified. First, detailed data on the efficacy of PFO-closure across different devices, particularly transition probabilities, is lacking. As a result, data from the GORE REDUCE study evaluating the GORE® CARDIOFORM Septal Occluder was used, as it contained sufficient contemporary, publicly available data. This device was used as a proxy for all such devices in our model, as the primary aim was to measure the costs and benefits of increased PFO diagnostic testing, rather than comparing specific PFO-closure devices. Moreover, to validate our proxy, we compared its effectiveness against the average estimated effectiveness of PFO-closure devices, demonstrating that the proxy accurately represents these devices.[12] Second, to calculate the outcomes of the decision tree, the sensitivity and specificity of TTE, TCD, and TEE were derived from the literature and included in the model. However, in the literature, the sensitivity and specificity of TTE and TCD were reported relative to TEE. To overcome this, the absolute sensitivity and specificity of TTE and TCD were calculated using the relative values of TTE and TCD and the absolute values of TEE. Third, this analysis assumed that patients who tested negative for TTE did not undergo a TEE to rule out other cardiac causes, where a PFO might be incidentally discovered. As this occurrence is considered uncommon, it was not incorporated into the analysis. Fourth, the accuracy of diagnostic tests depends on various factors, including operator expertise and adherence to protocols. However, this study assumes that adequate expertise is available and that tests are performed correctly. Fifth, the diagnostic testing rate for PFO in the real-world, modeled through the Current Diagnostic Scenario, can vary highly from provider to provider. To address this parameter uncertainty, we conducted multiple scenario analyses to explore the potential variation in the real-world setting. Sixth, we used the NMB to present the results of the DSA and scenario analyses. While NMB is a different outcome measure than the ICER—commonly used in cost-effectiveness analyses and the primary outcome in our base case—this choice limits direct comparability with the base case results. However, due to the occurrence of several negative ICERs in these analyses, NMB was considered the more appropriate and interpretable metric. Negative ICERs can be ambiguous, as they may reflect either a dominant or dominated situation. By using NMB, we avoided this ambiguity and ensured uniformity in result presentation within sensitivity analyses. To support interpretation and relation to the base case, we also included the base case NMB in the sensitivity analysis results. Last, this cost-effectiveness model focused on patients in the US that experienced a PFO-associated stroke, evaluated from a payor perspective. As a result, the findings may not be generalizable to other populations or healthcare settings. Additionally, although we aimed to reflect clinical practice as accurately as possible, economic models inherently simplify real-world care and cannot account for all individual variations and clinical complexities. The model was designed to represent the typical, average patient experience.

A key strength of our research lies in combining a decision-tree with Markov model, ensuring an accurate representation of real-world clinical pathways and outcomes. The decision tree illustrates the clinical pathway of patients from diagnosis until the treatment decision. Since the decision tree served as the input for the Markov model, which in turn calculated the health and economic implications of Optimal PFO Diagnostics, its robustness was essential. To ensure this robustness, both parts of the model underwent thorough internal and external validation by clinical experts. Furthermore, insights from prior CEMs comparing PFO closure with medical therapy were incorporated to strengthen the model's reliability and relevance[19,21].

To our knowledge, this is the first CEA that analyzes the effects of Optimal PFO Diagnostics to prevent recurrent strokes in US patients with a history of cryptogenic stroke. Recent research has demonstrated that PFO closure improves health-related quality of life[46] and is considered cost-effective compared to medical therapy alone[13] in cryptogenic stroke patients. Our findings align with these results and further highlight the benefits of PFO closure through enhanced PFO testing, optimizing patient outcomes and economic efficiency. Additionally, optimal PFO testing yields superior cost-effectiveness compared to increasing thrombolytic use for acute ischemic stroke treatment as reported in a cost-effectiveness study by Penaloza-Ramos et al. Considering a population of 100,000 patients, they found $46,000 of cost savings and 3.3 QALYs gained with increased thrombolytic use, while this study found $1.9 million of cost savings and 286 QALYs gained in a smaller population of 1,000 patients[47].

Conclusion

This study estimated that increasing diagnostic testing rates for PFO is a cost-effective strategy, leading to improved health outcomes for patients while saving costs. This is driven by more patients being appropriately diagnosed and treated with PFO closure, resulting in a considerable reduction in the expected number of recurrent strokes over time. Increased PFO testing may help prevent recurrent strokes, improve patient outcomes, reduce disability, as well as lower healthcare costs and hospital resource use.

Transparency

Declaration of funding

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Declaration of financial/other relationships

R.J.I. and E.J.L. are Associates of W.L. Gore & Associates, the study sponsor. T.L., G.T., and T.L. are employees of Asc Academics, which are consultants to the study sponsor. JJV and SEK have received grant funding from W.L. Gore and Associates. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

All the authors confirm that they were part of this study and have played a significant role from the conceptualization of the study to the article preparation. All the authors approved the final version of the article along with the author order as presented in the article. J.J.V. and S.E.K. provided clinical expertise on the scientific content and interpretation of the study. T.L., G.T., T.L., and R.J.I. contributed to the study conceptualization and design, data collection, data analysis, results interpretation, and article writing. E.J.L. contributed to study design, results interpretation and article writing.

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